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OPERATIVE TREATMENT OF THYROTOXICOSIS

I. PRIMARY RESULTS OF 608 THYROIDECTOMIES DURING THE PERIOD 1941—1950.

T. SVEND HANSEN, TH. FRIIS, FRITZ FUCHS and KURT IVERSEN.

During recent years the discussion regarding the treatment of thyrotoxicosis has increased after the therapeutic possibilities were extended to effective medical treatment with antithyroid substances and radioactive iodine.

In order to assess the value of these new methods, it is essential to know what surgical treatment can accomplish to-day. To this end we analysed a 10-year series of thyroidectomies for thyrotoxicosis, comparing the results with similar recent Scandinavian series.

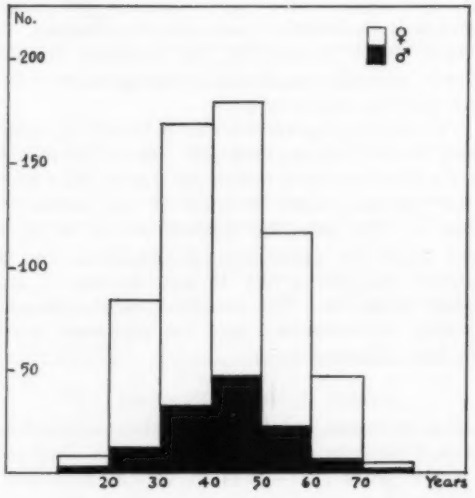

Fig. 1.
Age distribution.

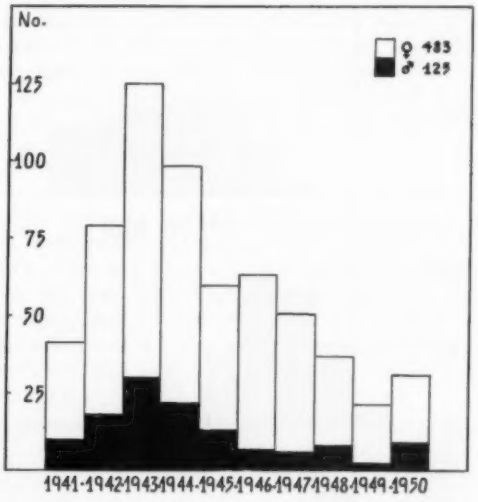

Fig. 2.
Distribution of operations over the 10-year period.

MATERIAL

The material comprises 608 patients with thyrotoxicosis operated upon during the period 1941—1950. Practically all age groups are represented (Fig. 1). The ratio of males to females is 1:3.9, rather surprising since most other series show a higher female preponderance.

During these 10 years the distribution of the operations is uneven (Fig. 2), there being a decided peak in 1943—1944, corresponding to the peculiar increase in the incidence of thyrotoxicosis in Denmark during the war, a phenomenon which has been discussed by Kurt Iversen (4).

The series includes patients with toxic diffuse goitre, toxic nodular goitre, recurrence of thyrotoxicosis following thyroidectomy, and recurrence of thyrotoxicosis following medical management — including a few patients who had received X-ray therapy (Table 1).

Most of the patients had primarily been admitted to a medical department from which they had in most cases not been transferred until

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Diffuse toxic goitre	476	78.4 %
Nodular toxic goitre	96	15.8 %
Recurrent toxic goitre (after surgical treatment)	13	2.0 %
Recurrent toxic goitre (after medical treatment)	23	3.8 %

Table 1.
Frequency of the various forms of toxic goitres in the material.

thoroughly prepared for surgery. In the majority of cases the preoperative treatment consisted merely in iodine medication, but during the latter part of the period 97 patients (18 per cent) received thiouracil preparations. For a minimum of one week before the operation, however, all patients received iodine alone.

In 80 per cent the B. M. R. had been brought down to below + 30 per cent before the operation. In the remaining cases it was higher, but the time of operation was decided on the basis of a clinical estimate of the patient's status — including weight gain and fall in pulse rate. Fig. 3 is a graphic illustration of the initial, the preoperative, and the postoperative B. M. R.

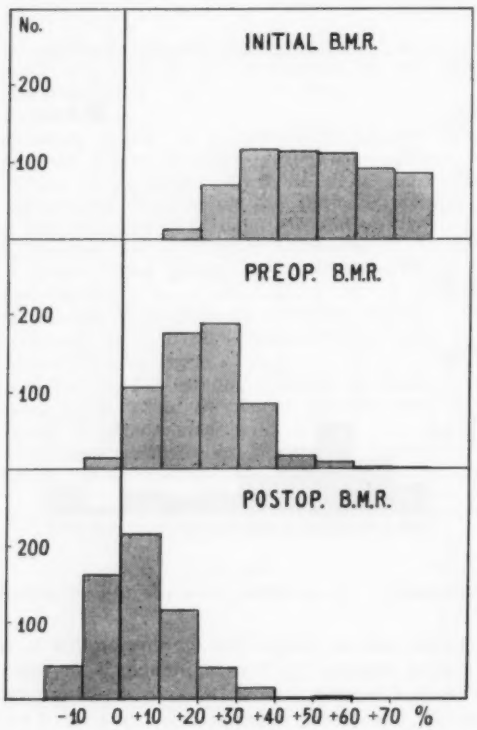

Fig. 3.
Distribution of initial, preoperative, and postoperative basal metabolic rates.

In 63 cases (10.4 per cent) the goitre was characterised as "large", in 323 (53.1 per cent) as "moderately large", and in 47 (28.8 per cent) as "small", whereas in 47 (7.7 per cent) there was no palpable enlargement of the thyroid gland. In 248 cases (40.5 per cent) the thyrotoxicosis was accompanied by more or less pronounced exophthalmos, unilateral in 20.

Great stress was laid on the preoperative evaluation of the cardiac status. Eighty-three patients (13.7 per cent) had ECG changes. The clinical classification of the heart diseases may be seen from Table 2.

Cardiac insufficiency	10	13.7 %
Cardiac insufficiency with arrhythmia	10	
Permanent perpetual arrhythmia	32	
Intermittent perpetual arrhythmia	10	
Other heart diseases	21	
No heart disease	525	86.3 %

Table 2.
Complicating heart disease.

In the early period the anaesthetic technique was usually plexus anaesthesia supplemented by local anaesthesia of the skin. Later barbiturate anaesthesia came into increasing use, and gradually as the anaesthetic department developed, all operations have been carried out under combined inhalation anaesthesia. During the period under discussion, 246 patients received plexus + local anaesthesia, whereas all the others had general anaesthesia.

The type of operation was subtotal thyroidectomy in 584 cases and subtotal hemithyroidectomy in 24. The operative technique was in brief transverse incision with division of the pretracheal muscles. The superior thyroid artery is ligated and cut at the upper pole of the gland, and the inferior thyroid artery is also ligated, if it is easily accessible. The resection of the gland is in part intracapsular, and the recurrent nerves are not dissected free.

RESULTS

The primary operative mortality was 0.8 per cent, 5 patients dying postoperatively — all during the years 1941—1944 in which there was a striking number of severe cases. Since then, there have been no postoperative deaths in 527 operations for thyrotoxicosis, *i. e.*, no operative mortality during the 11 years until the conclusion of this study in June 1954. Three of the postoperative deaths were due to peracute afterbleeding leading to death because of compression of the cervical viscera. One patient — a 47-year-old man — died on the 4th postoperative day in a state of hyperpyrexia and thyrotoxic crisis. Lastly, one patient, a 60-year-old woman, died showing signs of heart failure on the 3rd day after operation for a large retrosternal toxic goitre with severe tracheal compression. In addition, this patient had been suffering from heart disease and hypertension; autopsy revealed severe chronic nephrosclerosis and enormous hypertrophy of the heart.

The postoperative course was uneventful in 554 patients (91.1 per cent) except for short-lived elevations of temperature, discharge from the wound or other insignificant complications. In 26 instances there was major postoperative haemorrhage, necessitating re-operation to secure haemostasis in 25. Three of these patients died, as already mentioned. Four had postoperative thyrotoxic crisis, leading to death in 1 as mentioned above. Three patients developed pneumonia, one parotitis, and two exhibited signs of cerebral haemorrhage.

Clinically manifest tetany occurred in 8 cases (1.3 per cent), whereas latent tetany, manifesting itself as paraesthesiae, Chvostek's sign, etc. was evident in 10 (1.7 per cent). The results of the postoperative serum calcium determinations are given in Table 3.

Serum calcium		Clinical symptoms		
Below 7.9 mg %	20	Manifest tetany	8	1.3%
		Latent tetany	10	1.7%
8.0—8.9 mg %	38			
9.0—11 mg %	447			
Above 11 mg %	64			
Not determined	39			

Table 3.
Parathyroid function postoperatively.

The results of postoperative laryngoscopy — usually performed one week after the operation — may be seen from Table 4. Two patients had preoperatively exhibited unilateral paralysis of the recurrent laryngeal nerve, and one of them had bilateral paralysis after the operation. The subsequent course is unknown, as the patient had died from an intercurrent disease before the follow-up examination. Paralysis of the recurrent laryngeal nerve occurred in a total of 13 per cent before discharge.

Normal	483	79.5 %
Unilateral paralysis	76	12.5 %
Bilateral paralysis	3	0.5 %
No laryngoscopy	46	7.5 %

Table 4.
Postoperative laryngoscopic findings.

The duration of the postoperative stay in hospital is set out in Table 5. It shows that 86.7 per cent could be discharged a maximum of 3 weeks after the operation. Out of those patients who had not been discharged 4 weeks after the operation, a large proportion had other diseases unrelated to the thyrotoxicosis.

Less than 2 weeks	302	50.1 %
Between 2 and 3 weeks	221	36.6 %
Between 3 and 4 weeks	44	7.3 %
More than 4 weeks	36	6.0 %

Table 5.
Duration of stay in hospital after operation.

In Table 6 the primary operative results are compared with those of a few recent Scandinavian series. It is evident that operation for thyrotoxicosis following preoperative iodine medication carries a very low mortality. Apart from paralysis of the recurrent laryngeal nerve, the operative complications are moderate.

In a subsequent paper the authors will try to elucidate the late results of the operative treatment of thyrotoxic goitre (5).

SUMMARY

The primary results of 608 thyroidectomies for thyrotoxicosis during the 10-year period 1941—1950 are reported. The primary mortality was 0.8 per cent, paralysis of the recurrent laryngeal nerve occurred in 13 per cent, manifest tetany in 1.3 per cent, latent tetany in 1.7 per cent, and postoperative haemorrhage in 4.3 per cent.

	Number of patients	Operated on during the period	Primary mortality	Manifest tetany	Paralysis of recurrent laryngeal nerve
Windfeld (1940)	395	1926—35	2.8 %	?	?
Bertelsen et al. (1947)	910	1940—44	0.77%	1.1%	7.3%
Lundgren (1951)	467	1941—51	0.21%	?	?
Dollerup et al. (1953)	227	1941—50	3.0 %	2.2%	15%
Efskind et al. (1955)	718	1936—51	1.0 %	0.8%	1.8%
Thorén (1955)	434	1948—51	0.2 %	3.2%	9.4%
Present material	608	1941—50	0.8 %	1.3%	13%

Table 6.
The results of the present study compared with those of six recent Scandinavian materials.

References:

1) *Bertelsen, A. & E. Christensen:* Acta Chir. Scand. 1947, suppl. 133.
2) *Dollerup, E., C. J. Hansen & B. Mølgaard:* Nord. Med. 1953, *50:* 1161.
3) *Efskind, L. & C. Cappeln:* Acta Chir. Scand. 1955, *110:* 76.
4) *Iversen, Kurt:* Temporary Rise in the Frequency of Thyrotoxicosis in Denmark 1941—1945. Thesis, Copenhagen 1948.
5) *Iversen, K., T. Friis, F. Fuchs & T. Svend Hansen:* Dan. Med. Bull. 1957, *4:* 4.
6) *Lundgren, A.:* Transact. 25th Meeting Northern Surgical Assoc. 1951, p. 302.
7) *Thorén, A.:* Acta Chir. Scand. 1955, *110:* 151.
8) *Wijnbladh, H.:* Acta Chir. Scand. 1955, *110:* 129.
9) *Windfeld, P.:* Nord. Med. 1940, *8:* 2029.

OPERATIVE TREATMENT OF THYROTOXICOSIS

II. FOLLOW-UP OF PATIENTS OPERATED ON DURING THE PERIOD 1941—1950

By KURT IVERSEN, TH. FRIIS, FRITZ FUCHS and T. SVEND HANSEN

From 1941 to 1950 a total of 608 patients underwent operation for thyrotoxicosis in Surgical Department V of Kommunehospitalet, Copenhagen.

The primary operative results have been reported in the preceding paper (3). Here the results of a follow-up will be described. The follow-up period ranged from 4 to 14 years, with an average of 9.2 years.

All the patients were personally re-examined and their condition evaluated jointly by internist and surgeon. As far as possible, the re-examination also included, in addition to questioning and physical examination, a test of the fasting B. M. R. and determination of serum calcium as well as of protein-bound iodine. Lastly, laryngoscopy was performed whenever there was a possibility that paralysis of the recurrent laryngeal nerve might have been present.

Out of the original series of 608 patients, 5 died postoperatively. Three patients, who were euthyroid after the operation, have later succumbed to their thyrotoxic heart disease, sixty-one died of intercurrent diseases before the follow-up, and four have died of unknown causes. Lastly, one patient died after a Naffziger operation for malignant exophthalmos. Thus, seventy-four patients died before the follow-up which comprises 442, so out of the original series of 608 patients, we have obtained data for 516 (85 per cent).

This relatively low follow-up percentage must be considered on the background of the long follow-up period.

Frequency of Recurrence. In this analysis recurrence is taken to mean persisting thyrotoxicosis as well as subsequent, actual recurrences. A follow-up diagnosis of recurrence was based on a clinical estimate combined with the result of the metabolic test, the upper limit of normal being set at + 20 per cent.

A total of 17 patients (3.8 per cent) had a recurrence of thyrotoxicosis during the follow-up period. Half of them had re-operation and half of them medical treatment. At follow-up all these patients were completely cured.

Mild thyrotoxic recurrence was demonstrated at follow-up in a further 19 (4.3 per cent), so the total number of recurrences during the entire follow-up period was 36 (8.1 per cent).

Myxoedema. This diagnosis was also based on a clinical estimate combined with the metabolic values, the lower limit of normal being fixed as — 10 per cent.

During the follow-up period 36 patients (8.1 per cent) had myxoedema, transitory in 12 cases, whereas 24 required constant desiccated thyroid medication.

At follow-up a further 13 (2.9 per cent) were found to be suffering from myxoedema.

Thus, during the entire follow-up period, myxoedema had occurred in 49 patients (11.1 per cent), 37 (8.4 per cent) of whom were permanently afflicted.

Paralysis of the Recurrent Laryngeal Nerve. As already mentioned in the preceding paper (3), 13 per cent of the patients developed postoperative paralysis of the recurrent laryngeal nerve. At follow-up about half of them, *i. e.*, 5.6 per cent of the patients who had laryngoscopy, still exhibited unilateral paralysis of the recurrent laryngeal nerve. It must be mentioned, however, that 10 of the 76 patients with postoperative paralysis did not subsequently have laryngoscopy, either because they could not be traced or because they refused. Supposing that the paralysis was transitory in half of these patients too, the ultimate result is permanent unilateral paralysis of the recurrent laryngeal nerve in about 7 per cent.

Thirteen of the 25 patients with permanent unilateral paralysis had normal voices, whereas 11 were slightly and one very hoarse. In the great majority of cases, the paralysis was of no significance, although a few reported that the strenght of their voice was reduced.

Out of the three patients with bilateral postoperative paralysis one had died of an intercurrent disease and two could not be traced.

Tetany. Five of the eight patients with postoperative paralysis, one had died of an inter- this condition at the time of follow-up (1.1 per cent permanent tetany). Nevertheless, they were all fully capable of working, and no cataracts had occurred.

The results of the follow-up determination of serum calcium are given in Table 1.

Exophthalmos was demonstrated at follow-up in 16.7 per cent, severe in 0.7 per cent. The corresponding preoperative values were 40.5 per cent with 4.3 per cent severe. Two patients developed malignant exophthalmos after the operation.

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> 11 mg %	1.4 %
9.0—11 mg %	88.5 %
8.0—8.9 mg %	3.6 %
< 8.0 mg %	0.0 %
Unknown	6.5 %
5 patients treated for tetany	(1.1 %)

Table 1.
Serum calcium at follow-up.

A small *recurrence of the goitre* was found in 5.9 per cent and a larger recurrence in 1.1 per cent. In 2.3 per cent the recurrence was thyrotoxic.

In assessing the final results we classified the patients as shown in Table 2. "Fully cured" are those who were fully restored to health, subjectively as well as objectively, and fully capable of working, whose B. M. R., as determined in one ambulatory test, was between — 10 per cent and + 20 per cent. These criteria were satisfied by 74 per cent of the re-examined patients.

Furthermore, 2 per cent were "improved", *i. e.*, they were euthyroid, but had certain residual symptoms, such as heart disease or pronounced exophthalmos.

As already mentioned, follow-up revealed myxoedema in 2.9 per cent and recurrence of thyrotoxicosis in 4.3 per cent. In these cases, however, the hypothyroidism or hyperthyroidism was very moderate, not recognized by the patients themselves, but in our opinion treatment was indicated.

The "special" group comprises 74 patients (16.8 per cent) who were clinically euthyroid, subjectively cured and fully capable of working, but the B. M. R., determined in one ambulatory test, was below — 10 per cent in 9 and above + 20 per cent in 65. Of course, one ambulatory metabolic test is of limited value, but for practical reasons it could not be repeated. Since, clinically, these patients seemed to be completely cured, we feel justified in classifying them in the "cured" group which then includes 90.8 per cent in all.

In the course of the follow-up examination we questioned the patients regarding their personal opinion of the operative results. This questioning revealed that 79.2 per cent considered themselves completely cured and 16.1 per cent improved; 3.4 per cent stated that their condition was unchanged, and lastly 1.3 per cent thought that they were worse. As might be expected, these results are not identical with ours, some patients considering themselves cured although they had mild signs of thyrotoxicosis or hypothyroidism, while reversely others looked upon various uncharacteristic complaints as vestiges of the original disease or consequences of the operation.

Fully cured	74.0 %	
"Special" patients	16.8 %	
Clinically cured		90.8 %
Improved (euthyroid with residual symptoms)		2.0 %
Worse		0 %
Myxoedema		2.9 %
Recurrence		4.3 %

Table 2.
Results at follow-up.

DISCUSSION

In Table 3 we have compared the results of our follow-up study with those of some recent Scandinavian series.

Despite some variations between the series, the table shows what surgery can accomplish at present in the treatment of thyrotoxicosis.

After operation, recurrences must be expected in between 4 and 8 per cent, myxoedema in 6—8 per cent, and permanent tetany in 1—3 per cent.

In the series with the best results, the frequency of paralysis of the recurrent laryngeal nerve is below 2 per cent. In this respect Windfeldt's and our series, and presumably also Dollerup et al.'s, differ from the others, the frequency of this complication being considerably higher.

This is presumably due to the fact that in our series, and probably also in the other two Danish series, the operations were performed by a number of different surgeons, whereas in the others they seem to have been carried out by fewer and more experienced surgeons, a fact which must be assumed to reduce the frequency of this complication.

The ultimate results of surgical treatment are very similar in all the series, showing that oper-

	Number of patients followed up	Recurrence	Myxoedema	Tetany	Paralysis of recurrent laryngeal nerve	Fully cured or with slight residual symptoms
1. Windfeld 1940	340	10.6 %	8.5 %	2.2 %	13.2 %	90.6 %
2. Dollerup, Hansen et al. 1953	150	4.6 %	7.3 %	2.7 %	?	74.7 %
3. Thorén 1955*	414	3.9 %	7.6 %	1.4 %	2.5 %	84 %
4. Efskind 1955	607	6.4 %	5.4 %	0.8 %	0.7 %	89 %
5. Wijnbladh 1955*	430	3.7 %	7.7 %	1.1 %	1.5 %	85.8 %
6. Present series	442	8.1 %	8.4 %	1.1 %	7 %	92.8 %

Table 3.
Present series compared with five recent Scandinavian follow-up studies.
(Partly identical materials.)*

ation for thyrotoxicosis results in complete cure or cure with mild residual symptoms in 85—90 per cent. When also considering that the operative mortality is 1 per cent or less, surgery must be considered effective in the treatment of thyrotoxicosis.

SUMMARY

A total of 608 patients thyroidectomized for thyrotoxicosis during the period 1941—1950 were followed up.

During the follow-up period 74 patients had died. Of the remaining cases 442 were reexamined.

Of them 74 per cent were "fully cured", *i. e.*, subjectively and objectively fully restored to health and fully capable of working, with a B.M.R. of between — 10 per cent and + 20 per cent.

In addition, 2 per cent were "improved", *i. e.*, euthyroid, but suffering from mild residual symptoms.

Moreover, 2.9 per cent had myxoedema, 4.3 per cent recurrence of thyrotoxicosis, and 16.8 per cent were clinically euthyroid, subjectively cured and fully capable of working, but their B. M. R. was below — 10 per cent or above + 20 per cent. Patients of this latter category were considered as cured. Thus, at follow-up a total of 90.8 per cent were classified as cured.

References:

1) *Dollerup, E., C. J. Hansen & B. Mølgaard:* Nord. Med. 1953, *50:* 1161.

2) *Efskind, L. & C. Cappeln:* Acta Chir. Scand. 1955, *110:* 76.

3) *Hansen, T. Svend, T. Friis, F. Fuchs & K. Iversen:* Dan. Med. Bull. 1957, *4:* 1.

4) *Thorén, A.:* Acta Chir. Scand. 1955, *110:* 151.

5) *Wijnbladh, H.:* Acta Chir. Scand. 1955, *110:* 129.

6) *Windfeld, P.:* Nord. Med. 1940, *8:* 2029.

PROTEIN-BOUND IODINE IN PATIENTS OPERATED UPON FOR THYROTOXICOSIS

By TH. FRIIS, FRITZ FUCHS, KURT IVERSEN and T. SVEND HANSEN

In a follow-up of patients operated upon for thyrotoxicosis (6, 8), we determined the protein-bound iodine (PBI) in serum in the majority of the cases in order to assess the value of this method in estimating the clinical status.

PREVIOUS INVESTIGATIONS

According to previous investigations the concentration of PBI is useful in distinguishing between a hypothyroid, euthyorid, and hyperthyroid status (1, 2, 3, 4, 9, 12, 13, 14, 15, 16). Enhanced values have been found in 70—90 per cent of thyrotoxic patients, whereas reduced values are reported in 80—90 per cent of hypothyroid subjects.

The normal values range from 3½ to 8 μg per cent, mean value 6.12 μg per cent (4).

Little has been published regarding the PBI after thyroidectomy. Winkler, Riggs, Thompson & Man (18) report that in 37 patients thyroidectomized for thyrotoxicosis, the PBI fell to below 8 μg per cent within three weeks of the operation. In the same category of patients Lamberg, Wahlberg & Forsius (9, 17) also found a fall, in some cases even to subnormal values. They state that PBI is more valuable in estimating the clinical status than determination of the B. M. R. in ambulatory patients. According to Rapport et al. (12), PBI is of value in detecting postoperative hypothyroidism.

MATERIAL

The determination of PBI was carried out on venous blood by the method of Barker (2). Patients who had been receiving medicine containing iodine during the past three weeks and pa-

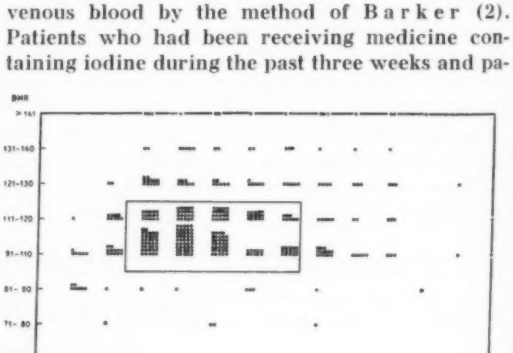

Fig. 1.

Correlation between PBI and B. M. R. in the entire series. Total PBI determinations: 396 = 89.6%. Total B. M. R. determinations: 389 = 88.0%. (The scale for the B. M. R. is different from that in the text. Thus 91—110 corresponds to —9 to + 10).

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tients who had, within the past year, had X-ray examinations with iodized contrast media, were not included in the test.

PBI was determined in 396 of the 442 patients (89.6 per cent) of the follow-up series (8). Determination of the B. M. R. was performed on an out-patient basis after 45 minutes' rest in 389 cases (88.0 per cent), and the analysis includes only the successful tests.

Fig. 1 correlates the B. M. R. and the PBI in the entire series. It is evident that some patients had increased metabolic rate and normal PBI and others normal metabolic rate and decreased or increased PBI.

	Number of patients	% of total series	Number of B.M.R. determinations	Number of analyses for PBI
1. Fully cured patients (B.M.R. between —10% and + 20%)	327	74.0%	275	289
2. Clinically cured patients with abnormal B.M.R.	74	16.8%	74	74
3. Improved patients, *i. e.*, patients who were clinically euthyroid, but who had a few thyrotoxic residual symptoms, such as *e. g.* exophthalmos	9	2.0%	8	9
4. Clinically hyperthyroid	19	4.3%	19	15
5. Clinically hypothyroid	13	2.9%	13	9
Total	442		389	396

Table 1. *Distribution of follow-up series.*

The patients are distributed as shown in Table 1. The classification was based on data given by the patients themselves and on their clinical status at follow-up, paying regard to the B. M. R., but not to the concentration of PBI.

The distribution of PBI in Group 1 (clinically cured with normal metabolic rate) is given in Fig. 2 which shows that 28 patients (9.7 per cent of those analysed in Group 1) had PBI values lower than 3¼ μg per cent. Furthermore, 42 patients (14.6 per cent of the analyses) exhibited values exceeding 8 μg per cent. Out of the latter 5 were pregnant, and presumably had increased PBI for this reason (5, 7, 10). Twenty-one patients were on desiccated thyroid medication, which can explain the enhanced values in 16 of them. In the remaining four the values were very high (>15 μg per cent), presumably owing to contamination of the blood specimens. This leaves 17 patients with values exceeding 8 μg per cent for unknown reasons, *i. e.*, 5.9 per cent of the analyses in this group. Some of these patients may have been taking medicine containing iodine without this being known.

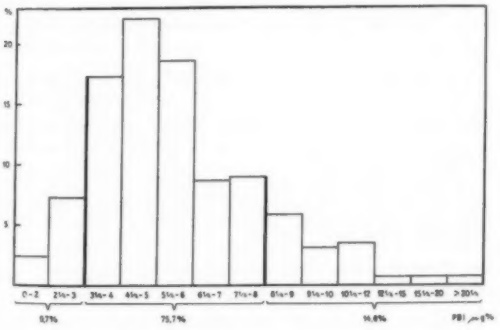

Fig. 2.

PBI in clinically cured patients with normal B. M. R. (Group 1). Total patients 327 = 74%. Total analyses 289. The heavy lines indicate the normal limits.

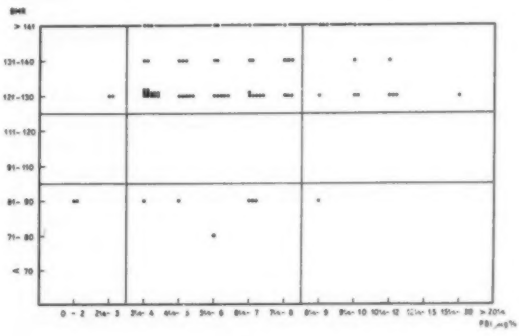

Fig. 3.

Correlation between PBI and B. M. R. determinations in clinically euthyroid patients with abnormal B.M.R. (Group 2). Total patients: 74. Total B. M. R. determinations: 74. Total PBI analyses: 74.

As far as Group 2 is concerned (clinically cured patients with abnormal metabolic rate), the relation between PBI and B. M. R. is shown in Fig. 3. Sixty-five patients (14.7 per cent of the entire follow-up series) had a B. M. R. exceeding + 20 per cent without any clinical signs of

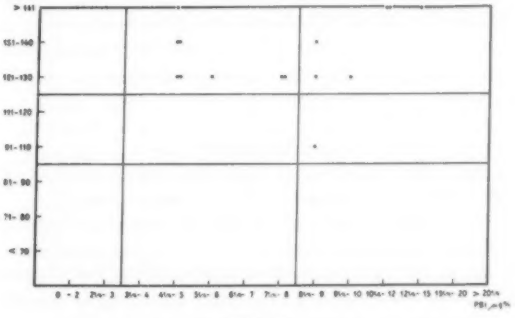

Fig. 4.

Correlation between PBI and B. M. R. determinations in clinically hyperthyroid patients (Group 4). Total patients: 19. Total B. M. R. determinations: 19. Total PBI analyses: 15.

thyrotoxicosis; nine (2.0 per cent) had a B. M. R. of less than — 10 per cent without clinical signs of hypothyroidism. The PBI values were distributed as follows: Four patients had PBI <3¼ µg per cent (5.4 per cent) and 14> 8 µg per cent (20.0 per cent). One had such a high value that contamination with iodine was likely. Two patients had a low B. M. R. as well as a low PBI and 13 had increased B. M. R. and PBI.

In Group 3 (clinically euthyroid patients with a few residual thyrotoxic symptoms) 4 had a B. M. R. exceeding 20 per cent and 3 had increased PBI. One of these high values was presumably due to contamination. Two patients had increased B. M. R. as well as increased PBI.

In Group 4 (clinically hyperthyroid patients) the correlation is set out in Fig. 4 which shows

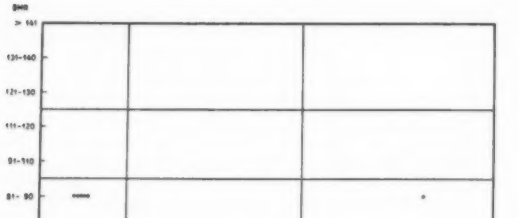

Fig. 5.

Correlation between PBI and B. M. R. determinations in clinically hypothyroid patients (Group 5). Total patients: 13. Total B. M. R. determinations: 13. Total PBI analyses: 9.

that 17 out of 19 patients had an enhanced B. M. R., whereas only 7 out of 15 had a PBI value exceeding 8 µg per cent. One of the patients with a normal PBI value had been receiving methylthiouracil, and this may have normalized the PBI.

In Group 5 (clinically hypothyroid patients) the correlation is given in Fig 5. All had a subnormal B. M. R., 6 had a low PBI, whereas in 1 it was normal and in 2 enhanced. The latter two were being treated by desiccated thyroid, which probably explains the increase.

DISCUSSION

In how many cases did the PBI accord with the clinical evaluation of the status?

Good agreement was found in the hypothyroid group (Group 5).

Less satisfactory agreement was found in the hyperthyroid group (Group 4). This does not accord with series of non-thyroidectomized patients. However, de Mowbray & Tickner (11) found that only 61 per cent of thyrotoxic patients had increased values.

In the group of "improved patients" (Group 3) 3 out of 9 had increased PBI. Two of them also had an increased B. M. R. and were possibly hyperthyroid.

Group 2 (clinically euthyroid patients with abnormal metabolic rate) contained 13 patients with increased PBI as well as B. M. R. Some of them have possibly been suffering from mild, clinically unrecognized hyperthyroidism.

It is striking that nearly 10 per cent of the thyroidectomized euthyroid patients (Group 1) had low PBI values and that 6 per cent had increased values for unknown reasons. As already mentioned, Lamberg et al. found that in some cases the PBI falls to subnormal values after operation, particularly in patients who have had exophthalmos before the operation.

Possibly, thyroidectomy is responsible for the low PBI in these patients, as the small portion of the gland which remains cannot keep up the usual concentration of PBI. This is perhaps also the reason why only half the hyperthyroid patients have enhanced values.

As a total result of our studies it may be stated that the result of the PBI test accorded with the clinical status in 79.8 per cent.

On the whole, therefore, the value of this test does not appear to be up to what has been reported in the literature apart from de Mowbray & Tickner's series (11). The discrepancy may, however, be due to the fact that the great majority of the reported series comprise non-thyroidectomized patients. It is our impression that the analysis constitutes a valuable supplement to determination of the B. M. R., but used alone it is insufficient for evaluation of patients operated upon for thyrotoxicosis.

SUMMARY

Protein-bound iodine was determined by the method of Barker in 89.6 per cent of 442 patients thyroidectomized for thyrotoxicosis 4—14 years previously. The B. M. R. was determined in 88.0 per cent.

In cured patients with normal B. M. R. the PBI was reduced in 9.7 per cent and enhanced in 5.9 per cent.

Of clinically cured patients with abnormal B. M. R., 5.4 per cent had reduced and 20 per cent increased PBI. Some of the latter may have been slightly thyrotoxic.

Among the thyrotoxic patients only half had increased PBI, whereas 6 out of 7 hypothyroid patients had low values.

References:

1) *Bandy, P. K. & B. C. Hallmann:* Am. J. Med. 1951, *11:* 619.
2) *Barker, S. B.:* J. Biol. Chem. 1948, *173:* 715.
3) *Blackburn, C. M. & M. H. Power:* J. Clin. Endocrin. 1955, *15:* 1379.
4) *Friis, Th.:* Acta Med. Scand. 1954, *149:* 463.

5) *Friis, Th. & E. Secher:* Acta Endocrin. 1955, *18:* 428.
6) *Hansen, T. Svend, Th. Friis, F. Fuchs, & K. Iversen:* Dan. Med. Bull. 1957, *4:* 1.
7) *Heinemann, M., C. E. Johnson & E. B. Man:* J. Clin. Invest. 1948, *27:* 91.
8) *Iversen, K., Th. Friis, F. Fuchs & T. Svend Hansen:* Dan. Med. Bull. 1957, *4:* 4.
9) *Lamberg, B.-A., P. Wahlberg & P. I. Forsius:* Nord. Med. 1954, *51:* 571.
10) *Man, E. B., M. Heinemann, C. E. Johnson, D. C. Seary & J. P. Peters:* J. Clin. Invest. 1951, *30:* 137.
11) *de Mowbray, R. R. & A. Tickner:* Lancet 1952, *II:* 511.
12) *Rapport, R. L. & G. M. Curtis:* J. Clin. Endocrin. 1950, *10:* 735.
13) *Saarenmaa, E.:* Acta Chir. Scand. 1955, *110:* 106.
14) *Salter, W. T., A. M. Basset & T. S. Sappington:* Am.
15) *Skanse, B.:* Nord. Med. 1955, *54:* 1419. J. Med. Science 1941, *202:* 527.
16) *Starr, P., D. W. Petit, A. L. Chaney, H. Rollman, J. B. Aiken, B. Jamieson & I. Kling:* J. Clin. Endocrin. 1950, *10:* 1237.
17) *Wahlberg, P., B.-A. Lamberg & P. I. Forsius:* Acta Med. Scand. 1956, *154:* 257.
18) *Winkler, A. W., D. S. Riggs, K. W. Thompson, & E. B. Man:* J. Clin. Invest. 1946, *25:* 404.

THE EMPLOYMENT OF ARTIFICIAL RESPIRATION IN DISEASES OTHER THAN POLIOMYELITIS

By ERIK HENRIKSEN

During the great epidemic of poliomyelitis which struck Greater Copenhagen in 1952, a significant number of patients suffering from respiratory paralysis were saved by treatment with tracheotomy, bronchial toilet and manual or mechanical positive pressure ventilation. The procedure has been described in a series of publications and the experience obtained is now collected in book form edited by H. C. A. Lassen (2). After the end of the epidemic it seemed natural to utilize the experience gained to the benefit of patients suffering from respiratory insufficiency from other causes.

By respiratory insufficiency is understood in the present paper the condition which develops when a patient, on account of inadequate ventilation, is no longer able to maintain maximum arterial oxygen saturation and/or cannot excrete the carbon dioxide formed by metabolism.

Acute or subacute respiratory insufficiency is encountered in conditions which are associated with obstruction of the respiratory passages, whether this obstruction be caused by secretion, membranes, swelling of the mucous membrane or oedema. Insufficiency of respiration may, similarly, occur in a series of conditions in the combined neuro-muscular respiratory apparatus; the disease may electively attack the central nervous system as in meningitis and encephalitis, more peripherally as in polyradiculitis or may attack the neuro-muscular end-plates as in myasthenia gravis. Where patients suffering from tetanus are concerned, the inadequate ventilation is a sequel of therapy with sedatives or curare.

Such radical therapy as tracheotomy and possibly prolonged artificial respiration should be reserved for patients in whom the respiratory insufficiency is produced by conditions which are either spontaneously reversible as, for example, polyradiculitis or accessible to therapy as in meningitis or tetanus.

The methods of recognizing respiratory insufficiency and its treatment are described in detail in the works on bulbar poliomyelitis previously mentioned and will therefore be referred to only in broad outlines.

The clinical condition will frequently suggest respiratory insufficiency; thus obstruction of the upper air passages manifests itself by inspiratory stridor together with retraction in the suprasternal notch, over the clavicles and in the epigastrium. In patients with cerebral lesions, failing of respiration may be encountered, possibly of the Cheyne-Stokes type, or only feeble respiratory movements; in the paralytic patient thoracic and/or diaphragmatic respiration may be absent, possibly combined with paradoxal respiratory movements.

In patients suffering from respiratory insufficiency, cyanosis, anxiety and restlessness indicate hypoxia, while increase of the blood pressure, sweating, accumulation of secretions in the respiratory passages and confusion are symptoms which are evidence of hypercapnia.

In a patient with inadequate ventilation, the further procedure depends upon the degree of hypoxia. Should this be considered to endanger life, the patient should immediately be intubated and subsequently tracheotomized and possibly artificial respiration performed. If, on the other hand, a more thorough observation is possible, suspicion of reduced ventilation should be verified by arterial puncture; the oxygen saturation is determined as a percentage of the maximum, and the pH and the total carbon dioxide content are determined after which the CO_2 tension may be calculated. If reduced oxygen saturation and/or low pH and high carbon dioxide tension are found

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in the arterial blood, these are indications for some form of therapy which can improve ventilation.

Patients suffering from hypoventilation and in whom the condition is dominated by neuromuscular respiratory insufficiency, are treated according to the same principles as the patients with poliomyelitis and respiratory paralysis. If the respiratory passages are "dry", *i. e.*, showing no accumulation of secretion, the patient is well suited for treatment in a tank or cuirasse respirator; if signs of stagnation of secretion develop subsequently, the treatment must be carried through according to the same principles as for patients in whom the respiratory passages are primarily "wet".

In such patients in whom respiration is compromized by accumulation of secretion, attempts are made to obtain a free airway, partly by the removal of secretion by suction with the assistance of a pulmonary physiotherapist and partly by positioning the patient to favour drainage. Overflow of gastric contents into the trachea is prevented by emptying the stomach; all attempts at swallowing are forbidden; fluid is administered parenterally at the beginning and later, when the stomach obviously empties normally, by means of a stomach tube.

When this treatment can be carried out, ventilation will be secured in some cases, but a number of patients with cerebral lesions develop a fall in blood pressure when placed in an effective position for drainage. If the treatment cannot be carried out, or if it does not result in adequate ventilation, tracheotomy is indicated.

As a main rule, tracheotomy is carried out under intubation and general anaesthesia; certain unconscious patients may, however, be tracheotomized under local anaesthesia. Through the tracheostoma an inflatable cuff-tube is introduced and through this bronchial toilet is carried out with simultaneous treatment by a pulmonary physiotherapist. When the respiratory passages are free, another attempt is made to see if spontaneous respiration is possible, if need be with oxygen administration.

If it is not possible following tracheotomy to obtain optimal oxygen saturation in the arterial blood and to eliminate respiratory acidosis, artificial respiration must be resorted to. In adults and older children a respirator may be employed (Engstrøm or Lundia respirator) while in infants so-called finger ventilation is employed. A number of the patients require continuous artificial respiration, while others only require assistance with every second or third spontaneous respiration, and for this purpose manual positive pressure ventilation must be employed.

The condition is frequently complicated by a fall in the blood pressure which must be treated in the usual way with blood transfusion, dried serum, Macrodex (Pharmacia, plasma substitute) or noradrenaline.

Employing the treatment described, it will be possible in the majority of cases, at any rate, to ensure adequate ventilation and to stabilize the blood pressure. Respite is thus obtained for treatment of the causal condition or anticipation of its spontaneous regression. As soon as the condition of the patient permits, the patient is gradually trained to return to spontaneous respiration. When swallowing is adequate the rubber tube is replaced by a silver cannula. If the causal condition has meanwhile been overcome, the silver cannula can also soon be removed.

MATERIAL

In the Hospital for Infectious Diseases in Copenhagen (Blegdamshospitalet) 51 patients with respiratory insufficiency have hitherto been treated according to the therapeutic principles recorded above (see Table 1).

Table 1.
Patients with respiratory insufficiency classified according to the causal condition to which the respiratory insufficiency was a complication.

	Total	Dead
Polyradiculitis	7	4
Tetanus	10	5
Tetanus neonatorum	7	7
Encephalitis	3	1
Purulent meningitis	7	5
Acute laryngitis	6	5
Infectious mononucleosis	2	0
Myasthenia gravis	2	0
Convulsions following aspiration	1	0
Carbon tetrachloride poisoning	1	1
Thrombosis of the basilar artery	1	0
Pyloric stenosis (shock)	1	1
Botulism	1	0
Disseminated sclerosis	1	1
Transverse myelitis	1	0
Total	51	30

The group of patients with respiratory paralysis on account of polyradiculitis constitutes the category which both clinical and therapeutically most resembles the group of poliomyelitis patients; there is, however, the decisive difference that the prognosis for the pareses is good if the acute phase is survived. Seven adult patients are concerned with massive pareses including respiratory paresis. Three of the patients were elderly individuals with complicating cardiac diseases, a circumstance which contributes significantly to the high lethality. Three patients were successfully treated, two have been discharged from hospital and are well while the third is still in hospital; the cannula has been removed and there are no symptoms from the respiratory organs; the other pareses are regressing under physiotherapy.

The largest group is that of the tetanus patients, a total of 17. Of these, 10 were adults or older children. In these patients, tracheotomy was a

prophylactic measure to prevent asphyxia on account of spasms of the larynx and to permit rapid and efficient ventilation should administration of curare be indicated on account of tetanic cessation of respiration.

The patients were treated according to the principles previously described from this department (1,3). In all cases, such deep anaesthesia was necessary on account of severe tetanus that spontaneous ventilation was inadequate and assistance ventilation or positive pressure ventilation with a respirator was necessary. The respiratory insufficiency was thus a direct sequel of the therapy employed.

The occurrence of 5 deaths among 10 patients does not answer to our expectations from this treatment. Two patients died from aplastic anaemia with secondary bacteraemia at a stage of their illness when the tetanus had run its course. This complication which appears to have developed as a sequel to the prolonged nitrous oxide anaesthesia which was employed (4) will probably be avoidable in the future. Three patients died from thrombo-embolic complications. In one, a young man, an infected thrombus was found in the right femoral vein where a polyethylene catheter had been introduced. On blood culture, bacteraemia with penicillin resistant staphylococci was demonstrated. The other two patients died from massive pulmonary emboli originating from phlebitis in the lower limbs. In these patients also, the phlebitis was caused by the continual infusions of fluid through polyethylene catheters. Hypertonic solutions had not been employed. There were no signs of bacteraemia.

In all 10 patients it was possible to control the tetanus by means of the treatment employed. The deaths which occurred must be regarded as complications of the very prolonged and exacting therapy. Inhibition of the bone marrow should be preventible in future. Continual infusion of fluids will be avoided as much as possible. Should, however, such infusions become necessary, energetic phlebitis prophylaxis with anticoagulation therapy and passive movements will be instituted from the start.

All seven patients suffering from tetanus neonatorum died. In one, the tracheotomy presented technical difficulties causing mediastinal emphysema and bilateral pneumothorax. In the remaining 6, atelectasis developed and persisted despite treatment, rendering ventilation impossible. Our last patients with tetanus neonatorum were therefore not tracheotomized and ventilated until vital indications developed.

The group with encephalitis comprises three patients. One of these was a boy with morbilli encephalitis. He developed cessation of respiration and required urgent tracheotomy and ventilation. Already after 6 hours could he return to spontaneous ventilation and after 48 hours the cannula could be removed. He was later discharged fully recovered.

Two young females with encephalitis of unknown etiology caused, however, great difficulties. Both patients lay in a deep coma for weeks. One of them had convulsions during which ventilation was necessary. She was successfully kept alive until the encephalitis regressed. She improved gradually but then developed a bronchopleural fistula complicated by pleural empyema. The patient was then transferred to a department for thoracic surgery. The pulmonary condition was overcome and it is known that she has recovered to such an extent that she could undertake a long journey abroad.

The other female patient with encephalitis developed cessation of respiration and required urgent tracheotomy and ventilation. The condition, despite the deep unconsciousness, was quite stationary for approximately a fortnight; thereafter a fall in the blood pressure occurred, resisting therapy with transfusions and norexedrin and the patient died.

It is perhaps surprising that in 7 patients suffering from purulent meningitis, tracheotomy and positive pressure ventilation was performed. In 6 cases pneumococcal or staphylococcal meningitis was concerned while one case of purulent meningitis was of unknown etiology. All patients were in a deep coma. The indication for tracheotomy was the accumulation of secretion and atelectasis. Artificial ventilation was necessary on account of reduced arterial oxygen saturation (values as low as 60 per cent were encountered). In these patients, particularly, the significance of hypoxia in the total clinical picture was striking when apparently moribund patients recovered when optimum ventilation had been secured. Frequently, however, the failing respiration was combined with other signs of failure of cerebral regulation with marked fall in blood pressure followed by oligo- or anuria which complicated the treatment greatly. The therapy instituted with tracheotomy and positive pressure ventilation evidently prolonged life and in one case, at any rate, the intervention proved life-saving.

Patients suffering from acute laryngitis were treated routinely with rest in bed, steam and penicillin. Tracheotomy may be necessary in very ill patients with cyanosis, stridor and deep retractions. Thereafter the respiration should, as a rule, be free and further treatment unnecessary. When a few patients were treated with positive pressure ventilation, it was because they had been hypoxic for such a long period that the respiration did not improve spontaneously when free air-way had been obtained or because the condition was complicated by membranous tracheobronchitis with changes extending far down in the bronchi, impeding effective spontaneous ventilation.

The fact that positive pressure ventilation is rarely indicated in patients suffering from acute laryngitis should be apparent from the observation that in the period in which 6 patients required ventilation, 892 patients suffering from acute laryngitis were treated in the department.

Two patients with infectious mononucleosis were tracheotomized and ventilated on account of mechanical respiratory obstruction produced by membranous inflammation of the mucosa extending down into the bronchial tree.

The table includes two patients with myasthenia gravis, both young people who hitherto had managed well or fairly well, respectively, on drug therapy but in whom, in connection with catarrhal infection and acute bronchitis, the weakened muscles of respiration became so overtaxed that respiratory insufficiency occurred, and this could not be overcome by increasing administration of prostigmin or by toilet of the upper respiratory passages. Following tracheotomy and ventilation, the condition improved rapidly, the catarrhal condition was cured in a few days and the patients could resume normal ventilation and soon be discharged in the same condition as prior to the acute infection.

Finally, a girl of 19 years suffering from botulism will be mentioned. This patient was admitted with paresis of the eye muscles and of swallowing. Some days later, respiratory insufficiency developed. Following tracheotomy and positive pressure respiration she calmed down. The subsequent course was uneventful and the pareses gradually regressed. After the elapse of approximately one month the tracheal cannula could be removed and shortly after she was transferred to another hospital for physiotherapy.

DISCUSSION

In recent years the significance of ensuring optimal ventilation particularly during pyrexial diseases in which the metabolism is greatly augmented has been increasingly appreciated. Measures to maintain the respiratory passages clear are undertaken routinely in the treatment of the disease. Secretion is removed by suction, and unconscious patients are placed in positions suitable to ensure drainage, tongue forceps being employed if required. If necessary, intubation is performed. If the coma proves to be of prolonged duration or if the drainage position is contra-indicated, as is frequently the case in patients with cerebral lesions, tracheotomy may be indicated (5).

In the Hospital for Infectious Diseases, Copenhagen (Blegdamshospitalet), we have followed these principles, but in a series of patients it was impossible to achieve optimal ventilation despite the ensuring of clear respiratory passages; such patients were, in addition, treated with artificial respiration. The treatment was carried out on 51 patients all of whom were so ill that vital indications for artificial ventilation were present.

In the patients suffering from tetanus neonatorum, treatment was unsuccessful in so far that it has hitherto been impossible to prevent the development of severe atelectasis. In the remaining 44 patients, definite improvement was observed in nearly all cases when the ventilation became optimal and hereby respite was obtained for the treatment of the causal condition or for its spontaneous resolution. In the 21 surviving patients the treatment must be regarded as life-saving in practically all cases. Hitherto this exacting treatment has been instituted with reluctance and it has been undertaken as a last resort. In future, if treatment is commenced before general failure of cerebral regulation has developed and if greater experience in routine, preventing the occurrence of complications is gained, it may be anticipated that an even greater percentage of these patients will survive.

SUMMARY

On the basis of the experience gained in the treatment of patients suffering from respiratory paresis due to poliomyelitis, a series of patients with respiratory insufficiency from other causes were treated with tracheotomy and artificial ventilation. Fifty-one patients were treated and twenty-one recovered.

References:

1) *Bjørneboe, M., B. Ibsen* and *S. Johnsen:* U. f. L. 1953, *115:* 1535.
2) *Lassen, H. C. A.* (ed): Management of Life Threatening Poliomyelitis. E. and S. Livingstone, London 1956.
3) *Lassen, H. C. A., M. Bjørneboe, B. Ibsen* and *F. Neukirch:* Lancet 1954, *I:* 1040.
4) *Lassen, H. C. A., E. Henriksen, F. Neukirch* and *H. Sund Kristensen:* Lancet 1956, *I:* 557.
5) *Lehmann, H.* and *A. B. Raper:* Brit. Med. J. 1956 *I:* 333.

THE EFFICACY OF BCG-VACCINATION

TUBERCULOSIS EPIDEMIC IN A STATE SCHOOL WITH AN OBSERVATION PERIOD OF 12 YEARS

By TAGE V. HYGE

An interesting illustration of the protective value of BCG-vaccination is provided by a rather unusual tuberculosis epidemic observed in a Danish state school for young girls (Aurehøj). This epidemic has now been followedup for more than 12 years, and the findings made have been described in several reports published between 1943 and 1956.

The epidemic in many respects resembled a controlled experiment. It involved 105 initially tuberculin-negative, 133 BCG-vaccinated and 130 initially tuberculin-positive girls, nearly all of whom were exposed to the same massive infection under the same conditions.

Both the schoolchildren and the staff had been repeatedly examined for tuberculosis — for the last time in early December 1942 — when the explosive and serious tuberculosis epidemic started in January-February 1943. The exposure to infection assumed a particularly massive character, as it took place in a blacked-out, badly ventilated air-raid shelter (a basement room also serving as a schoolroom).

The epidemic may be contrasted with another outbreak occurring in a light and airy school in June, 1939, which showed only a limited spread of infection.

A high incidence of infection was observed in the classes that were instructed in the air-raid shelter by the source case, a tuberculous female teacher suffering from a cold with sneezing and coughing (in Fig. 1 these forms are indicated by an asterisk). A number of girls who were not instructed by the infectious teacher but who came to the school-room immediately after she had given lessons there, were also infected.

The girls in one form completely escaped infection although they were taught in the air-raid shelter; they were, however, only instructed there during the early hours of the morning before the infectious teacher had arrived.

Evidently a droplet infection predominated.

The forms receiving no instruction in the basement room completely escaped infection.

The follow-up showed that the girls who developed primary tuberculosis with positive gastric lavage did not become infectious. Thus, they never infected their tuberuclin-negative younger brothers and sisters.

As in the source case, infectiousness was determined by the presence of a destructive (cavitary) lesion.

1) Of the *105 tuberculin-negative girls,* 94 of whom were exposed to the infection, 70 converted to positive (*i. e.,* their reaction to an intradermal Mantoux test with 10 TU or, in some instances, 100 TU changed from negative to positive).

41, or 58.6 per cent, of the convertors developed *primary tuberculosis* demonstrable by radiography and/or by gastric lavage. In addition, the following tuberculous manifestations were observed in connection with the primary infection: erythema nodosum in 8 cases, pleurisy in 10 cases (from 3 to 11 months after the primary infection) and exudative pericarditis and peritonitis in one case each.

During the 12 years' follow-up, post-primary pulmonary tuberculosis was diagnosed in 14 convertors, 8 of whom showed cavitation. In all but one convertor the post-primary disease was preceded by a demonstrable primary affection.

Thus, *post-primary tuberculosis of the lungs* developed in 15 per cent of those exposed, in 20 per cent of the convertors and in about 33 per cent of the girls with demonstrable primary tuberculosis.

In 3 cases only, the post-primary affection seemed to have arisen from the primary lesion.

In 6 cases the post-primary tuberculosis appeared within 6—12 months of the primary infection, and in 8 it occurred after an interval of 1—10 years (2 occurring after one year, 1 after two years, 1 after four years, 1 after five years and 3 after ten years), cf. Fig. 1.

The post-primary affection appeared between the ages of 15 and 24 years, arising at the age of 18 years in five cases, an indication of the increased susceptibility at the age of puberty.

One girl succumbed to a generalized dissemination of the disease after 3 years of severe illness.

2) Of the *133 BCG-vaccinated girls,* 106 of whom were exposed to the same intense infection — and under the same conditions — as the tuberculin-negative girls, only 2 developed progressive pulmonary tuberculosis, *i. e.,* 1.9 per cent of those exposed. In both girls the disease appeared one year after the epidemic, at the age of 16 and

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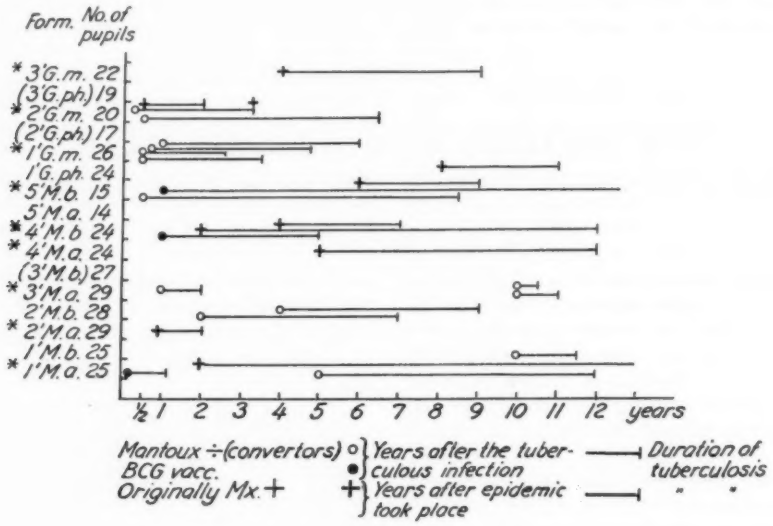

Fig. 1.
Time of onset and duration of post-primary tuberculosis. A 12 years' follow-up.

17 years, respectively. Both showed cavitation. No case of primary tuberculosis was observed among the BCG-vaccinated girls. Also, the 12 years' follow-up, which included full-sized radiography, revealed no further case of post-primary tuberculosis in this group.

One revertor, *i. e.*, a girl whose tuberculin reaction had changed from positive (following BCG-vaccination) to negative, was infected and developed a benign pulmonary tuberculosis of short duration (gastric lavage positive).

When a BCG-vaccinated person develops tuberculosis, it may often be due to such a reversion from positive to negative and thus to a lowered resistance against tuberculous infection.

Frequently the BCG-vaccinated have been only incompletely retested — or not at all, making it difficult to judge their immunity previous to an infection. Also, the infection may have taken place soon after vaccination before the specific immunity has developed.

Finally, in some cases an exogenous reinfection may occur despite successful BCG-vaccination. An example of this are the two afore-mentioned BCG-vaccinated girls with post-primary disease.

Compared with the tuberculin-negative group, about 46 cases of primary tuberculosis and at least 15 cases of post-primary tuberculosis should have appeared in the BCG-vaccinated group. Expressed as a percentage of the number of girls exposed, the incidence of post-primary pulmonary tuberculosis was 15 per cent in the tuberculin-negative group as against 1.9 per cent in the BCG-vaccinated group, that is, a ratio of 8:1.

These statistically significant differences in tuberculosis morbidity clearly demonstrate that BCG-vaccination confers protection not only against primary tuberculosis, but also against the late post-primary pulmonary tuberculosis.

3) Among the *130 originally tuberculin-positive girls*, 105 of whom were exposed to the infection, 9 cases of progressive post-primary pulmonary tuberculosis appeared during the 12 years of observation — corresponding to 8.6 per cent of the exposed. The date of infection in these cases cannot be determined with any accuracy, but it can be concluded that the interval between infection and the onset of the disease ranged from at least 6 months to more than 8 years. (Fig 1).

This group may be compared with the tuberculin-negative group; they are all convertors and the majority of the tuberculin-positive girls undoubtedly had been infected before the epidemic and outside the school.

The girls with post-primary disease represent latent cases of pulmonary tuberculosis that have flared-up presumably because of a lowering of resistance at the age of puberty (endogenous reinfection).

The possibility that a few cases were due to superinfection (exogenous reinfection) cannot be excluded since the exposure was particularly massive, as demonstrated by the high incidence of infection among the tuberculin-negative girls.

It is seen that those who become spontaneously tuberculin-positive incur greater risks than those who, while tuberculin-negative, are vaccinated with a potent BCG-vaccine that gives strong and lasting protection.

The afore-mentioned observations are presented graphically in Figs. 1 and 2.

There are 23 cases of post-primary pulmonary tuberculosis in the tuberculin-negative and the

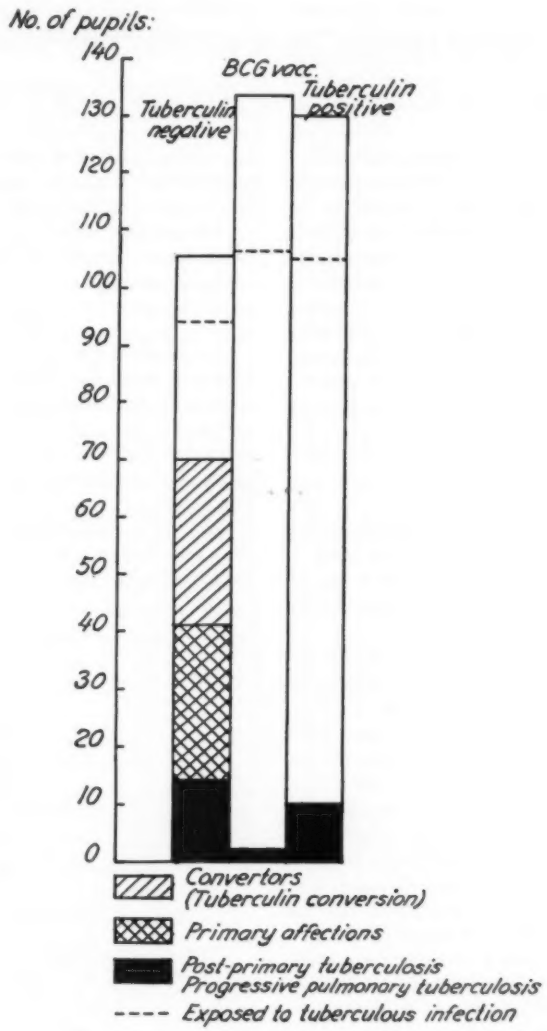

Fig. 2.
The results of exposure to tuberculous infection in the three groups described in the text.

tuberculin-positive groups combined against only 2 cases in the BCG-vaccinated group.

There are 8 times as many cases of post-primary pulmonary tuberculosis in the tuberculin-negative group as in the BCG-vaccinated group (15 per cent of the exposed against 1.9 per cent of the exposed); and the total incidence of tuberculosis (primary + post-primary, *i. e.*, 42 cases) is 23 times as high among the tuberculin-negative as among the BCG-vaccinated (44.6 per cent against 1.9 per cent).

The "experimental" school epidemic has thus clearly shown that the person most effectively protected against tuberculous infection and its possible consequences — primary and early or late appearing post-primary pulmonary tuberculosis — is the non-reactor who is vaccinated in time with a potent BCG-vaccine that produces a strong and lasting allergy.

References:

A more detailed account (with references) has been published in:

Hyge, Tage V.: Acta tuberc. scand., 1947, *21:* 1.
Hyge, Tage V.: Ugeskr. Læger, 1953, *115:* 1003.
Hyge, Tage V.: Acta tuberc. scand., 1956, *32:* 89.

PETHIDINE FOR ENDOSCOPIES

By S. H. JOHANSEN, H. RUBEN, A. GAMMELTOFT and H. K. KRISTENSEN

When anaesthesia is needed for endoscopies, the aim of the anaesthetist is to remove discomfort and provide good examination conditions at minimal risk to the patient. General anaesthesia as well as local analgesia are in current use, but neither seems to provide the ideal answer to these demands.

In the search for a suitable method, pethidine (demerol, meperidine, isonepecaine, dolantin) was suggested by the authors (1, 2, 3). Since the preliminary reports, pethidine has been employed for endoscopies in adult patients (4, 5), and the resulting experience is presented here.

TECHNIQUE

Premedication is unnecessary and should never be given, especially since the combined effect of pethidine and morphine or, even more so, of pethidine and a barbiturate may cause severe depression of the respiration (6).

After positioning of the patient, 50 mg of pethedine in a 1 per cent solution*) (5 ml) is injected slowly into the vein, the weak solution being used to ascertain a slow injection rate. The effect on the patient is assessed and, if necessary, additional doses of 15—25 mg are added. When the swallowing reflex, as provoked by touching the base of the tongue with the finger, has been abolished, the patient will be ready for endoscopy. The total amount of pethidine used in our cases has varied between 70 and 150 mg, depending on the reaction of the patient and the type of endoscopy. The maximal effect of the pethidine is obtained in 3—4 minutes and lasts at least 15 minutes, which has proved sufficient for procedures of this kind.

During the endoscopy the patients are awake and cooperative, though drowsy and frequently dizzy. Their reactions are typical of the analgesic stage of general anaesthesia (7, 8). After the procedure they may go to sleep and amnesia for the examination is not uncommon.

During the analgesia the respiration is usually unaffected but a moderate slowing up may be seen. The pulse rate is often slightly increased. The blood pressure keeps constant in the majority of cases, provided the horizontal position is maintained, but a lowering may occur, especially if the patient has a deficient blood volume (9).

Out-patients were kept in hospital 3—4 hours after the analgesia and were not allowed to leave unaccompanied.

RESULTS

The method has now been in use for more than 6 years and the total number of endoscopies carried out under pethidine analgesia amounts to 1939. All the patients have been adults. Apart from the fact that the cystoscopies have been performed on male patients, the cases have been unselected.

The endoscopies performed have been: Direct laryngoscopies, bronchoscopies, oesophagoscopies, gastroscopies and cystoscopies (Table 1).

Table 1.
Specification of 1939 endoscopies performed under pethidine analgesia.

	Pethidine alone	Pethidine + topical analgesia	Pethidine + general anaesthesia	Total
Laryngoscopies	43	120	0	163
Bronchoscopies	14	208	0	222
Oesophagoscopies	633	41	2	676
Gastroscopies	144	3	0	147
Cystoscopies on males	576	120	35	731

The effective dose of pethidine used for oesophogoscopies, gastroscopies and cystoscopies has averaged 100 mg, whereas approximately 125 mg has been necessary to produce analgesia for laryngoscopies and bronchoscopies.

Although it is possible to carry out the various procedures under pethidine analgesia alone, we soon learned that for bronchoscopies and direct laryngoscopies the reflex activity is not sufficiently suppressed without the additional application of topical analgesia (Table 1). The amount of local analgesia required is, however, noticeably reduced, if applied after the induction of the pethidine analgesia.

For oesophagoscopies and gastroscopies pethidine proved sufficient in the majority of cases (Table 1).

In cystoscopies on male patients the analgesia was not sufficient in 6 per cent of the cases and general anaesthesia had to be resorted to. For this reason some of the surgeons preferred supplimentary application of topical analgesia in the urethra. Still 73 per cent of the cystoscopies were performed with pethidine alone. In 24 instances

*) 4 ml of the officinal solution of pethidine (5 %) is diluted with 16 ml of physiological saline.

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electrocoagulation of papillomatas of the bladder was succesfully carried out under pethidine analgesia.

There has been no immediate or delayed death in the material attributable to the use of pethidine. In two instances an overdosage occurred, one due to an unexpected sensitivity following 50 mg, the other due to a faulty injection of 500 mg instead of, as intended, 50 mg. Both cases were succesfully treated with oxygen and n-allyl-normorphine. A case of a severe fall in blood pressure was encountered in an elderly male who was under treatment with reserpine for hypertension. Immediate administration of oxygen and a vasoconstrictor agent restored the blood pressure to normal levels. As the incidence of patients undergoing pharmacological antihypertensive treatment is steadily increasing, this complication must be warned against (10).

For the above reasons pethidine analgesia should never be induced unless means of resuscitation (oxygen, bag and mask, etc.) are ready at hand.

There has been one death following a perforation of the oesophagus during an apparently uneventful gastroscopy. The patient died 11 days later from mediastinitis.

COMMENT

In comparing general anaesthesia with the analgesia induced with pethidine in the manner described, the latter may in fact be considered no more than a last minute premedication, given intravenously, with avoidance of the general anaesthesia, thus obviously placing a smaller burden on the patient. Therefore also the technical risks which a general anaesthesia entails, especially in endoscopies through the pharynx, are not encountered during pethidine analgesia. Though in the hands of a skilled anaesthetist the use of a muscle relaxant will provide very good examination conditions, this can never be considered an innocent technique. In the hands of the inexperienced it is too dangerous to be employed at all.

A common method af analgesia used for cystoscopy is spinal analgesia, preferably a saddle block. Although this is a reliable technique, it carries the inconvenience of occasional headache, and the introduction of foreign material into the subarachnoid space represents a potential source of infection or intoxication, the result of which may be disastrous to the patient (11). Caudal analgesia is in these respects safer, but the incidence of failures is never less than 10 per cent, and the amounts of local analgesia required have produced general toxic reactions.

Many endoscopists and anaesthetists prefer topical analgesia which is considered safer than general anaesthesia. That the administration of a local analgesic, however, is not without danger is well realised. Thus, Avery Jones (12) reported 6 cases of toxic reactions, 4 of which were fatal, in a series of 49,000 gastroscopies under cocaine analgesia. If the local analgesia proves insufficient, the patient will struggle during the endoscopy, and a dangerous situation may arise.

The advantages of pethidine analgesia rest upon the fact that it is possible to keep the patient in an analgesic stage throughout the procedure and at the same time preserve his full cooperation. His vital functions are reasonably unimpaired while his reflexes are obtunded. In areas of great reflex activity it is recommendable, as previously mentioned, to add a local analgesic, but the reduced amounts needed will decrease the risk of a toxic reaction. The dose of pethidine is within the normal therapeutic range, and as the maximal effect is reached shortly after the intravenous injection and lasts for about 15 minutes, untoward reactions can be dealt with immediately, and the effect will be wearing off as the examination is about to finish.

Thus the risks of this method of analgesia are small compared with those of other techniques from a pharmacological as well as from a technical point of view.

Patients who have undergone repeated endoscopies under pethidine analgesia have been without fear of the subsequent performance, and those who have had occasion to compare the method with that of local analgesia alone, have preferred pethidine.

SUMMARY

The experience gained from 1939 cases of pethidine analgesia for endoscopic procedures has demonstrated that this method is reasonably safe to the patient compared with other methods from a pharmacological as well as from a technical point of view. This is so because the effective dose of pethidine is within the normal therapeutic range and because the technique is simple. During the endoscopy the patients are awake and cooperative and at the same time in a condition which facilitates the examination.

It is suggested that this method should be taken into consideration when analgesia for laryngoscopy, bronchoscopy, gastroscopy, oesophagoscopy or cystoscopy in the adult patient is discussed.

References:

1) *Ruben, H.:* Brit. J. Anaesth., 1951, *23:* 33.
2) *Gammeltoft, A., S. Johansen & H. Ruben:* Ugeskr. Læger, 1951, *113:* 525.
3) *Kristensen, H. K.:* Nord. Med., 1952, *47:* 561.
4) *Gammeltoft, A., S. Johansen & H. Ruben:* Ugeskr. Læger, 1953, *115:* 1448.
5) *Andersen, H. C., O. Jepsen & K. Sørensen:* Acta Oto-Laryngologica, 1954, *44:* 57.
6) *Møller, K. O.:* Ugeskr. Læger, 1952, *114:* 1785.
7) *Vonow, P.:* Der Anæsth., 1954, *3:* 88.
8) *Artusio, J. P.:* JAMA, 1955, *157:* 33.

9) *King, B. D., J. D. Elder & R. D. Dripps:* Surg. Gyn. & Obst., 1952, *94:* 591.
10) *Coakley, C. S., Seymont Alpert & John S. Boling:* J.A.M.A., 1956, *161:* 1144.
11) *Payne, J. P. & S .E. Bergentz:* Lancet, 1956, *1:* 666.
12) *Jones, F. A.:* Report from Medical Research Council no. 50/556. London 1950.

STUDIES ON A NEW LONG-ACTING INSULIN ZINC METHYLALBUMIN INSULIN

By OLE SKENSVED

INTRODUCTION

Insulin is freely soluble at the pH of blood and is therefore absorbed within a few hours. In order to obtain a retarded absorption and consequently a prolongation of the therapeutic effect over a period of up to 24 hours, the insulin must be slowly liberated at pH 7.

Of the different methods of producing such a "depot" preparation, it is worth mentioning Hagedorn et al.'s (1) and Krarup's (2). By these methods insulin negatively charged at pH 7 is combined with protamine extracted from fish sperm which is positively charged at the same pH. The protamine is not antigenic. Of other basic proteins, histones and globins (MacBryde & Reiss (3), Bailey & Marble (4)) have been used.

Scott & Fischer (5) found that the depot effect of protamine insulin could be further prolonged by the addition of zinc.

The latest development is the advent of insulin-zinc suspensions in an amorphous and/or crystalline state in an acetate buffer not containing zinc percipitating ions and without the addition of proteins (Hallas-Møller et al. (6)).

It seems strange that for 20 years only the naturally occurring basic proteins have been used to obtain the depot action. The fact is that they have been interpreted as the only available media that were not at the same time antigenic, but this is not so.

Human albumin is *eo ipso* a non-antigenic well-defined substance. Its reaction is acid, but a methylation process blocks the acid groups so that the methyl albumin behaves as a basic protein. Accordingly, it may be bound to the acid insulin, thus forming an insulin preparation slightly soluble at pH 7.

The use of human albumin is attractive, and the incidence of allergic reactions to this preparation might be imagined to be reduced compared with previous retardation media.

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Zinc Methyl-Albumin Insulin was kindly supplied by Roskilde Medical Company Ltd., Roskilde, Denmark.

ZINC METHYL-ALBUMIN INSULIN

The insulin component of this preparation is obtained from the pancreas of slaughtered animals and the albumin component from human serum purified at Statens Seruminstitut, Copenhagen, Denmark.

One litre of zinc methyl-albumin insulin (ZMAI), 40,000 international units, contains: 1.74 g insulin, 1.74 g methyl albumin, 16 g glycerol, 1.5 g tricresol, 0.6 g phenol, 80 mg zinc. Its pH ranges from 6.8 to 7.3.

The preparation is made from re-crystallized insulin containing not less than 24,000 i. u. per gramme.

Test for Antigenity of Methyl-Albumin.

To this end the author used the method advocated *e. g.* by Nathan and Kallos (7): 0.01 ml of the test substance is injected intracutaneously. One week later the intracutaneous injection of the same dose is repeated. If the substance is antigenic, cutaneous manifestation of sensitization will definitely appear within 24 hours of the second injection.

Forty-nine adults were tested by this method by a diluted solution of methylated human albumin. None of them exhibited skin reactions after the second injection.

CLINICAL TESTING

Material.

During a certain period all diabetics admitted to the department, in whom insulin was indicated, were adjusted to the preparation to be tested. This gave a total of 22 patients (7 men and 15 women), most of whom were admitted for diabetes which had been out of control — with or without insulin.

It will be seen from Table 1 and 2 that the material is fairly representative with the exception that it regrettably does not include children.

Method.

It was endeavoured to control the patients who had previously been receiving insulin on their usual preparation. If they remained out of control it was in most cases attemped to adjust them to other insulins. The blood sugar (Bs) was determined at 8 a. m. (fasting), 11 a. m., and 4 p. m.

Table 1.
The Material.

Age (years)	Duration of diabetes (years)	Duration of insulin therapy (years)
< 20: 3	< 5: 7	< 5: 6
21—40: 2	5—10: 6	5—10: 5
41—60: 9	> 10: 6	> 10: 4
> 60: 8	newly detected: 3	started during study: 7
min: 17		
max: 75		
Average: 51	max: 16	max: 16

Table 2.
Insulin doses.

	Previos dose of insulin (best obtainable)		ZMAI (in brackets fresh cases)		Decrease in units on ZMAI	Increase in units on ZMAI	Unchanged
	Once daily	Twice daily (or mixed)	Once daily	Twice daily			
Units	(No. of pat.)		(No. of pat.)				
12-20	2	0	2 (+2)	0	8 cases from 36 to 4 units, (average 17.5 units)	3 cases, 4 units, (average 4 units)	4 cases
21-40	1	1	3 (+4)	0			
41-60	4	1	7 (+1)	1			
60	2	4	2	0			
			average: 38 units in the 24 hours				

Then the patients were adjusted to ZMAI — in 21 cases 1 daily injection at 8 a. m..

Being stabilized on the new preparation with a fixed dose, the following analyses were made for 5 consecutive days: Bs at 8 and 11 a. m., at 4, 6, and 10 p. m., and at 2 and 5 a. m. Urinary sugar excretion in 4 portions: from 8 to 11 a. m., from 11 a. m. to 4 p. m., from 4 to 10 p. m., and from 10 p. m. to 8 a. m. This will be called the *5-day clinical test.*

In 3 cases where, for personal reasons, the patients had to restrict their stay in hospital as far as possible, we had only a little less than 5 days with determinations of Bs at 8 a. m., 11 a. m., and 4 p. m. and of the 24-hour urinary excretion of sugar (Us. D.).

During the 5-day test all the patients were ambulatory and, so far as their condition permitted, had ample exercise throughout the day.

Diet.

Practically all the patients had a full diet less sugar, caloric value 1500—3500 with a carbohydrate content of from app. 100 to a little over 300 g daily (the latter being rare). Only in 1 case, in which the control was poor, was it endeavoured to obtain improvement by weighed amounts of bread and potatoes. In a few cases, moreover, the mutual size of the individual meals and their carbohydrate content were changed according to the schedule given by Duncan (8).

The patients were instructed to take, as far as possible, the same amount and kind of food every day. The results would no doubt have been better if they had been given an accurately and weighed diet as done by *e. g.* Hallas-Møller (9) and Duncan (8). However, the author made a point of testing the preparation under conditions as close as possible to the "home pattern".

Re-adjustment from Previous Preparation to ZMAI.

As a rule, this was accomplished without major difficulties. Occasionally, however, the patients showed increased 24-hour urinary sugar excretion and a higher Bs at 8 and 11 a. m. and lower at 4—6 p. m. during the first days, but this was in most cases stabilized within 4—6 days.

RESULTS

In order to make the evalution as varied as possible, the author selected the following factors among those which influence the character of diabetic control:

(1) Mean blood sugar for the 24 hours determined in the case of ZMAI by calculating the mean of 7 daily determinations for 5 consecutive days (m. Bs. D5).
(2) Mean of daily maximum and minimum of blood sugar (determined as the mean of 5-day values, *e. g.* at 8, 11 a. m., etc.). The distance between the maximum and minimum m. Bs. is called Δ Bs.
(3) Mean urinary sugar excretion for 5 days (m. Us. D5).
(4) Persistent insulin reactions — or possible insulin shock.
(5) The extent to which the mean blood sugar curve for 5 days is representative. The fact is that extremely varying values from day to day and from hour to hour may easily give a "beautiful" m. Bs. curve, but without any relevance to the clinical applicability of the preparation.

This was endeavoured by calculating $S\gamma$ — the standard error — uncertainty on the mean value for each of the 7 Bs. values obtained in the 24 hours for the 5 consecutive days on the basis of the formula $S\gamma = \sqrt{\frac{\xi\ (x \div \bar{x})^2}{n \times (n \div 1)}}$. Thus, it is impossible to arrive at a final value for the 24-hour period and this quantity cannot be fitted into Table 3, but the $S\gamma$ values are given on the curves to supplement the evaluation. (It must be mentioned that if only a small number of determinations is made, $S\gamma$ will be relatively high and vice versa).

On the basis of (1), (2), (3), (4), and on an estimate of (5), the classification is set out in Table 3.

In Table 4 each patient is characterised exclusively by the poorest result obtained with regard to items one to five in Table 3. For example, a case with findings in the groups (1), (2), (3):

Table 3.
Classification of results on ZMAI and on other insulins.

m. Bs. D.	Max. m. Bs.	Min. m. Bs.	△ Bs.	Persistent minor insulin reactions	Sy	m. Us. D.	Classification
< 150	200	100	< 100	no	Acc. to	< 5 g	excellent
< 175	230	80	< 150	no	estimate	< 15 g	good
< 200	260	70	< 190	no		< 25 g	fair
< 210	300	70	< 230	yes		< 50 g	not sufficient
> 210	> 300	80	> 230	yes		> 50 g	poor

excellent and in group (4): bad, would be classified as bad.

The 15 patients who had been controlled with one or perhaps more insulin preparations before being started on ZMAI are, with a few exceptions, only represented by m. Bs. determined at 8 a. m., 11 a. m., and 4 p. m. as well as m.Us.D. Where the results on the former preparations are compared with those on ZMAI, the corresponding values are given for the latter.

As regards the 9 patients who had previously received another insulin and who are classified as excellent, good, and fair (vide infra), the findings were as follows: In no case was the control on ZMAI poorer than on a previous preparation, in 3 cases it was equally good on ZMAI once daily as on a previous preparation twice daily, in 1 case it was equally good on ZMAI once daily as on a previous preparation once daily. In 2 cases the control was far better and in 2 cases a little better on ZMAI once daily than on a previous preparation twice daily, and lastly in 1 case it was better on ZMAI once daily than on a previous preparation once daily.

The results on ZMAI were distributed as shown in Table 4.

Table 4.
Results on ZMAI.

excellent	good	fair	total	not sufficient	poor	total
5	6	4*)	15	5**)	2***)	7

*) 2 had not been tested on another insulin.
2 had been "not sufficient" on another insulin.
**) 2 had not been tested on another insulin.
1 had proved not sufficient on the best of other insulins.
2 were classified as poor on another insulin.
***) 1 was classified as not sufficient on the best of other insulins.
1 was classified as poor on a number of other insulins.

Excellent results are exemplified in Fig. 1 (Case XIX), good results in Fig. 2 (Case XXI), fair results in Fig. 3 (Case XIII).

Below a few details will be given regarding cases classified as (1) not sufficient (not suff.) and (2) poor.

Re (1): not sufficient.

Case V: ♀ aged 57, difficult to control, with high Δ Bs. as well as high m. Bs. D. and a tendency

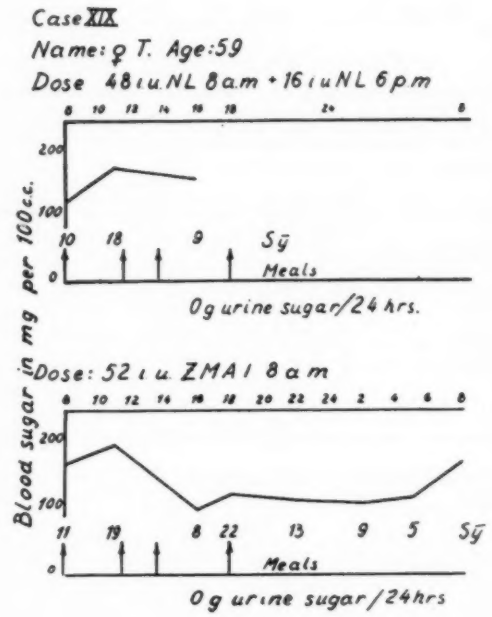

Fig. 1.

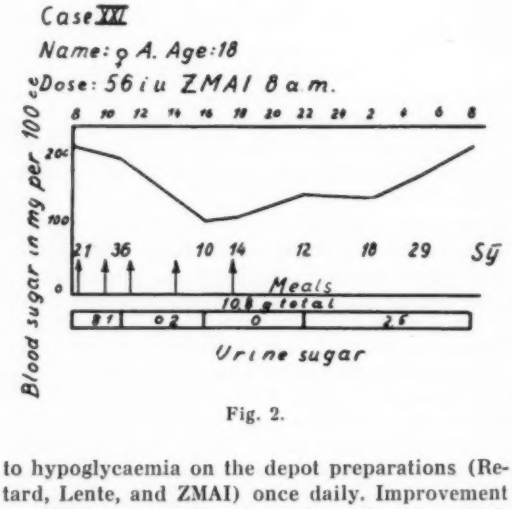

Fig. 2.

to hypoglycaemia on the depot preparations (Retard, Lente, and ZMAI) once daily. Improvement on ZMAI twice daily, the only patient in which this was necessary.

Case IX: ♀ aged 22, with prolonged diabetes, overdosed on 60 + 60 units of insulin Retard

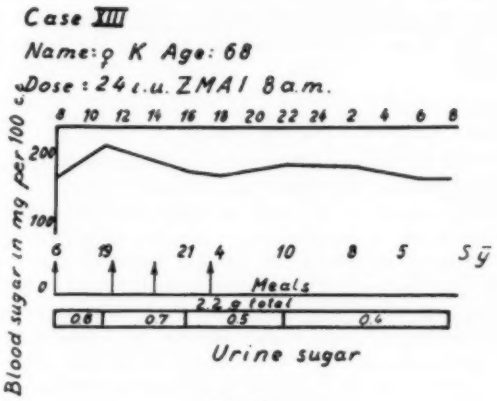

Fig. 3.

Discharged on 56 units of ZMAI with a high Δ Bs. Despite warnings, her food intake was extremely irregular.

Case XII: ♂ aged 63, who had not previously been treated with insulin. Exacerbation owing to infected hydronephrosis which had not entirely subsided, when the patient was controlled on 24 units of ZMAI daily.

Case XVII. Fig. 4: ♀ aged 60, admitted in precoma with coronary occlusion and renal damage. Discharged on 80 units of ZMAI once daily.

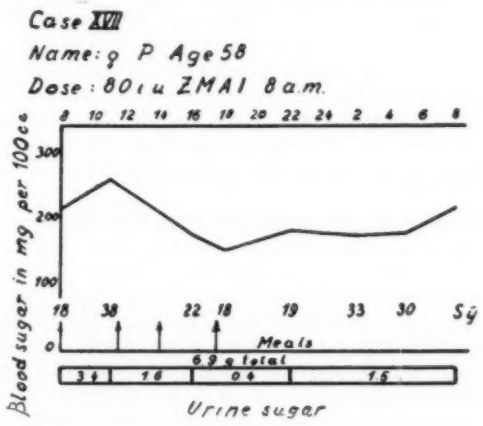

Fig. 4.

Case XVIII: ♀ aged 47, with recently discovered diabetes in a patient who discharged himself before satisfactory control had been achieved. 48 units once daily upon discharge.

Re (2): 2 cases classified as poor.

Case III: ♀ aged 17, with juvenile diabetes, difficult to control with different insulin combinations, also with ZMAI. Discharged on Novo Lente, 44 units, which gave somewhat better results than ZMAI.

Case VIII: ♂ aged 61, who was extremely difficult to cope with and who had previously been admitted 15 times. Numerous insulins and combinations of insulins had been tried with almost equally poor results. Discharged on insulin Retard, 52 units, as the patient felt best on this preparation.

These two last-mentioned patients were the only ones who had to be discharged on a preparation other than ZMAI.

Subsequently we have learned from a diabetic hospital that a third patient has abandoned ZMAI, now being controlled on a depot preparation + regular insulin in the morning and depot preparation in the evening. The rest of the series, *i. e.*, 19 patients, are still being controlled on ZMAI more than 2 years after the end of the present trial.

Duration of Effect.

On the basis of all 22 mean blood sugar curves, the duration of the effect of ZMAI may be estimated as an average of 21—24 hours, the minimum being about 18 hours and the maximum presumably in many cases more than 24 hours.

Maximum Effect: Usually between 4 and 12 p. m., but in a few cases later, *i. e.*, between 2 and 4 a. m. or perhaps sustained until this juncture.

Initial Effect: As a general rule it may be said that breakfast causes a (usually moderate) increase in Bs., an increase which has been wholly or partially eliminated at 4 p. m.

Considering the relatively marked depot effect of ZMAI, it could not be expected that breakfast would fail to manifest itself in the blood sugar values.

Insulin Reactions.

Actual insulin shock, *i. e.*, remoteness to unconsciousness, did not occur in the clinical ZMAI material, but in one case on another insulin. In one case on the ZMAI 5-day test, an insulin reaction occurred once or twice daily (and also daily on other preparations). This also happened in another case while on ZMAI once daily (and in the same case on another two preparations) but not on 2 daily injections. A third case had a very mild insulin reaction on one occasion (more distinct on another four preparations). Lastly, a fourth case had insulin reactions on other preparations, but not on ZMAI, on which the Bs. level was higher than on other preparations.

The tendency to these reactions might be said to be the same as on other preparations of the same nature.

Allergic Reactions.

None of the patients exhibited allergic reactions to ZMAI, but one to Insulin Novo Lente. This patient has later been adjusted to other preparations in another hospital where cutaneous tests had shown allergy not only as previously to Novo Lente, but now also to ZMAI. No allergy had been demonstrated to insulin Retard — (zinc allergy?)

SUMMARY

The preparation tested in the present study is Zinc Methyl-Albumin Insulin (ZMAI), an insulin bound to zinc and non-antigenic human albumin rendered basic by methylation. It was expected to give similar results with regard to depot effect as other insulin preparations whose depot effect is obtained by binding to another basic protein and in some cases also to zinc.

The series comprises 22 patients. The results obtained with ZMAI were classified as follows: excellent 5 cases, good 6, fair 4 — a total of 15. Furthermore, 5 were not sufficient and 2 poor. Out of the 5 cases classified as not sufficient 2 did not have other preparations, while 2 were worse and 1 remained not sufficient on other preparations (but slightly better than on ZMAI). Of the 2 patients classified as poor on ZMAI, one was also poor on other preparations (but slightly better) and the other one was not sufficient on another preparation. Out of the 15 patients who had previously received another insulin, 9 were classified as excellent, good, or fair on ZMAI. In none of them was the control poorer on ZMAI.

The duration of the effect averaged 21—24 hours. In most cases the maximum effect was found between 4 p. m. and midnight, in a few cases somewhat later. Slight insulin reactions were found in 3 cases. No allergic reactions were observed to ZMAI in the present series, although one patient subsequently showed cutaneous reactions to ZMAI in another hospital (zinc allergy?).

Out of 22 patients tested with ZMAI, 20 were discharged from the hospital on this preparation. One has subsequently abandoned it. The remaining 19 patients are still being controlled on ZMAI more than 2 years after the end of the present trial.

CONCLUSION

On the basis of the present findings it seems justified to conclude that ZMAI is an advance with regard to the way in which its depot effect has been accomplished, *i. e.*, by using human albumin. Moreover, its clinical effect in controlling diabetes might be said to be on a level with that of other long-acting insulins, in this series often better, more rarely poorer. It is also worth mentioning that its clinical use does not appear to give rise to essential untoward reactions.

References:

1) *Hagedorn, H. C., B. Norman Jensen, J. Wodstrup, N. B. Krarup:* JAMA, 1936, *106*, 177.
2) *Krarup, Niels B.:* The Action of Protamine Insulinate, G. E. C. Gad, Copenhagen, 1935.
3) *MacBryde & Reiss:* Journ. Clin. Endocrinology, 1944, *4:* 469.
4) *Bailey & Marble:* JAMA, 1942, *118:* 683.
5) *Scott, D. A. & A. M. Fischer:* Journ. Pharmacol. and Exp. Therap., 1935, *55:* 206.
6) *Hallas-Møller, K., M. Jersild, K. Petersen & J. Schlichtkrull:* Dan. Med. Bull., 1952, *1:* 249.
7) *Nathan & Kallos:* Arch. f. Dermatol., 1932, *167:* 129.
8) *Duncan, Garfield G.:* Metabolism., 1952, *1:* 108.
9) *Hallas-Møller, K.:* Insulin Novo, Booklet, Copenhagen, 1953.

URIC ACID IN THE CEREBROSPINAL FLUID

THE RELATIVE CONCENTRATION IN MENINGITIS AND OTHER NEUROLOGICAL DISORDERS

By CHRISTIAN CRONE

It is well-known that the transition of substances from the plasma to the cerebrospinal fluid is increased when the meninges are infected. It has thus been shown that the sulfonamides penetrate more readily from the general circulation in cases of purulent or tuberculous meningitis (Roelsen & Simesen 1942). The same is true of streptomycin (Lassen & Jensen 1948) and also — though less constant — of penicillin (Kinsman & d'Alonzo 1946). This increased permeability renders it possible in most instances to avoid the intraspinal application of antibacterial drugs.

Besides its therapeutic significance, the showing of an increased permeability is of a certain diagnostic interest, especially in the differential diagnosis of benign serous meningitis and the tuberculous serous meningitis, a fact that has been particularly stressed by Lassen (1942).

Estimation of the increased permeability is especially dependent on determining the relationship between the concentration in the cerebrospinal fluid and in the plasma for a number of foreign substances introduced into the organism (sulfonamides, streptomycin, etc.), but it is well-known that the ratio for certain preformed substances is also changed when the meninges are infected. This is true of proteins and glucose, but the changes in the relative concentration of these substances in the cerebrospinal fluid can not directly show an increase in the penetration of substances from the blood to the cerebrospinal fluid.

Uric acid has a very low concentration in the cerebrospinal flud, and it is one of the naturally

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Table 1.
The cerebrospinal fluid/plasma uric acid ratio in 16 cases of purulent meningitis.

Subject	Age years	Bact.	Cell-count	Protein-conc. mg%	Glucose conc. mg%	Uric acid conc. mg% C.S.F.	Uric acid conc. mg% plasma	Ratio %
H. L.	7/12	meningococ	2000/3	160	59	2.4	6.9	35
J. H.	2	Pfeiffer	100/3	32	53	0.7	2.9	24
C. A.	40	pneumococ	11000/3	240	24	2.0	4.5	45
G. J.	37	pneumococ	4300/3	420	24	1.5	2.5	60
B. S.	18	?	22000/3	420	18	1.8	4.4	41
L. H.	7	Pfeiffer	18000/3	450	18	1.9	3.7	51
L. N.	26	meningococ	78000/3	530	—	1.7	3.4	50
K. H.	2	meningococ	9000/3	50	60	0.9	3.0	30
V. J.	11	pneumococ	10000/3	110	74	0.3	2.7	11
F. P.	9	meningococ	21000/3	170	39	1.2	4.5	27
L. R.	2	meningococ	16000/3	430	28	2.5	7.0	26
I. C.	36	meningococ	110000/3	356	18	2.5	2.9	86
I. I.	12	Pfeiffer	300/3	65	46	0.5	1.9	26
G. R.	3	Pfeiffer	64000/3	180	17	2.8	5.0	56
B. V.	18	meningococ	17000/3	200	23	1.5	5.1	29
T. N.	43	?	25000/3	230	—	5.6	12.7	44

appearing diffusible substances which has the smallest cerebrospinal fluid-plasma ratio. It seems, therefore, of interest to investigate whether the ratio for this substance increases when the meninges are involved in a pathological process. That interest shown uric acid in this connection has hitherto been restricted, is probably due to the somewhat unspecific methods of analysing uric acid, which made it impossible to determine the very low uric acid concentrations in the cerebrospinal fluid to any degree of precision. The appearence of a specific enzymatic method for uric acid analysis (Prætorius 1949) justifies an examination of the problem, which is the purpose of the present work. Lous (1956), using the Prætorius method, has determined the normal ratio for uric acid and found it to be approximately 10 per cent and never above 15 per cent.

MATERIAL

Patients with various forms of meningitis (tuberculous, purulent and serous) were examined, in addition to patients with a number of different neurological disorders. The plasma- and the cerebrospinal fluid samples were taken simultaneously, in most cases when the patients entered the hospital. The uric acid was analysed with the aid of differential spectrophotometry (Prætorius and Poulsen 1953). At times when it was impossible to examine the samples immediately, they were stored at —20° C. For the analysis of cerebrospinal fluid, 1—2 ml liquor was generally used.

RESULTS

a) Table 1 shows the results for 16 cases of purulent bacterial meningitis. It is evident that the meningeal permeability of uric acid is considerably increased, the ratio being augmented in all cases but one.

b) That the ratio is also considerably increased in cases of tuberculous meningitis is shown in Table 2, from which it further emerges that treatment of the disease results in diminished permeability of uric acid.

Table 2.
The cerebrospinal fluid/plasma uric acid ratio in three cases of tuberculous meningitis.

Subject	Age years	Cell-count	Glu-cose ratio %	Uric Acid conc. mg % C.S.F.	Uric Acid conc. mg % plasma	Ratio %	Duration of antitu-berculous treat-ment in days
M. C.	1	608/3	20	1.5	2.0	75	0
W. C.	42	940/3	18	1.4	3.3	42	2
"	"	64/3	22	1.0	3.2	31	84
Y. Y.	6	192/3	24	1.4	2.5	56	116
"	"	134/3	73	0.7	2.5	28	226

c) The condition in cases of primary, serous meningitis is shown in Table 3, which lists the results from cases with a pronounced cell count. The ratio-values indicate a slight increase in the meningeal permeability.

Table 3.
The cerebrospinal fluid/plasma uric acid ratio in 5 cases of primary serous meningitis.

Subject	Age years	Cell-count	Glu-cose conc. mg. %	Uric acid conc. mg% C.S.F.	Uric acid conc. mg% plasma	Ratio %
F. J.	18	2100/3	34	1.2	5.5	22
B. A.	39	1500/3	69	0.8	3.2	25
T. A.	12	900/3	51	0.6	2.7	22
J. S.	16	1300/3	61	0.7	6.0	12
S. S.	8	1100/3	69	0.8	3.8	21

d) The permeability of uric acid has also been examined in a number of patients with various neurological disorders. Table 4 shows the generally "negative" results of this investigation. It appears that a disease such as disseminated sclerosis is not accompanied by a change in the meningeal permeability of uric acid. A moderate — but indubitable — increase of the cerebrospinal fluid — plasma ratio for uric acid is found

Table 4.
The cerebrospinal fluid/plasma uric acid ratio in various neurological disorders.

Subject	Diagnosis	Protein conc. mg% in C.S.F.	Uric acid conc. in C.S.F. mg%	Uric acid conc. in plasma mg%	Ratio
R. W.	Neuromyopathia thyreopriva	154	0.6	4.1	15
I. N.	Dementia (postencephalitica?)	176	0.6	3.8	16
M. M.	Tumor medullae spinalis	ca. 1000	1.0	5.6	18
R. T.	Radiculitis, obs. pro	44	0.5	4.8	10
N. F.	Encephalomyelitis disseminata	22	0.3	4.7	6
E. R.	Sclerosis amyotrofica lateralis	32	0.4	4.0	10
C. C.	Encephalopathia athetotica	20	0.5	4.6	11
C. J.	Tumor medullae spinalis	102	0.3	3.1	10
T. W.	Neurosis depressivus	24	0.2	2.5	8
E. P.	Cephalalgia	42	0.4	4.0	10
C. L.	Glioblastoma hemisfærii dxt.	93	0.4	3.9	10
F. G.	Epilepsia cryptogenetica	41	0.4	4.6	9
M. L.	Lues cerebrospinalis antea	45	0.6	5.5	11
I. G.	Encephalomyelitis disseminata	27	0.2	3.1	7
H. G. H.	Meningo-encephalomyelitis luica	?	1.2	5.1	24
H. A. J.	Radiculitis, obs. pro	126	0.9	6.5	14
H. P. H.	Arachnoiditis spinalis	72	1.4	6.4	22
H. S.	Encephalitidis seqv.	25	0.5	4.4	11
J. J.	Encephalitis acuta	280	1.4	5.5	25
J. I.	Sclerosis disseminata	68	0.5	5.6	9
N. S.	"	46	0.3	3.9	8
E. M.	"	42	0.3	3.4	9
E. B.	"	43	0.4	4.4	9
G. N.	"	125	0.7	3.6	20
T. J.	"	40	0.3	4.4	7
D. P.	"	46	0.7	6.5	11
K. F.	"	20	0.3	3.0	10
M. K.	"	42	0.4	4.3	9
T. I.	"	31	0.1	1.5	7

in cases of acute encephalitis, arachnoiditis and in a case of syphilitic meningo-encephalitis (with positive Wassermann fluid reaction), every one a case of infectious nature.

DISCUSSION

These investigations concerning the relationship between the uric acid concentration in cerebrospinal fluid and in plasma in different types of meningitis substantiate what others have found with respect to certain drugs: that there is an increased penetration of substances from the blood to the cerebrospinal fluid when the meninges are infected. It appears that the uric acid ratio is of use in measuring the degree of this increase in permeability. The present material does not, however, allow of any conclusions as to the permissibility of using the uric acid ratio as a quantitative measure of the increase in permeability.

In cases of purulent meningitis, there is a considerable increase in meningeal permeability estimated by the uric acid ratio, exactly as in cases of tuberculous meningitis; the other types of serous meningitis, however, only show a fairly moderate increase of the permeability. Bacterial infections thus augment the meningeal permeability to a substantially greater degree than the virus infections. Conditions in cases of acute encephalitis cannot be judged with any certainty on the basis of this material.

The tables show that there is some positive relation between the increased penetration of uric acid and the increase in the concentration of cerebrospinal protein content. More surprising is the connection between an increase of the uric acid ratio and a reduction of the cerebrospinal glucose concentration as is shown in Fig. 1.

In the case of acute meningitis, low sugar content of the cerebrospinal fluid is due to the glycolytic action of the organisms concerned, as proved experimentally by Merritt & Freemont-Smith (1938). It is hard to suppose the bacteria to be responsible for the increased uric acid concentration, and even if it appears that a low glucose concentration and an augmented uric acid ratio go together, the two phenomena must probably be differently explained. Whatever the explanation might be, increased meningeal permeability, it seems, is followed by reduced glucose concentration.

It is tempting to explain the low normal uric acid ratio (about 10 per cent) by a high protein-binding of uric acid in the plasma (or the existence of polymerised, non-diffusible forms). But it has, in fact, never been possible to prove this by ultrafiltration experiments. Such experiments have, on the contrary, shown uric acid to be completely or almost completely diffusible (Bene & Kersley 1951, Berliner, Hilton, Yü & Kennedey 1950). If these in vitro studies reflect the situation in vivo, one must suppose a selective secretion of urate ions from the plasma

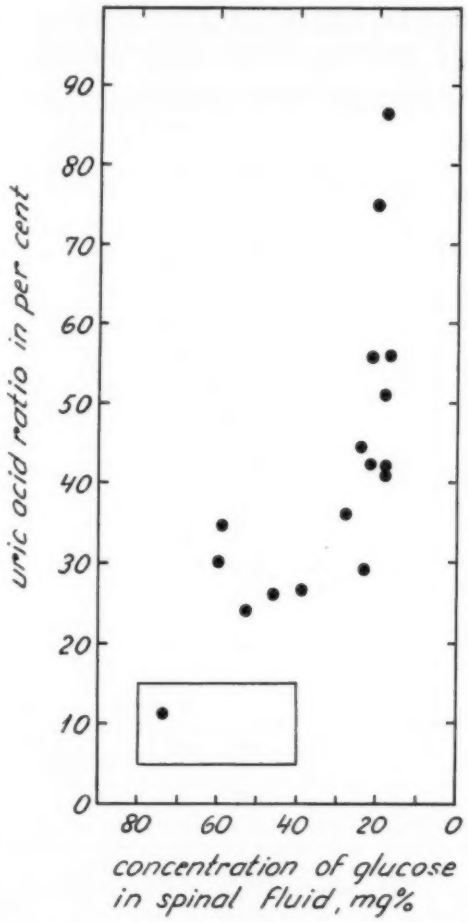

Fig. 1.
The uric acid ratio plotted against the concentration of glucose in the cerebrospinal fluid in 17 cases of purulent or tuberculous meningitis. The box indicates the normal limits.

into the cerebrospinal fluid, and that the mechanism normally restraining free passage of uric acid is damaged in cases of meningitis.

Schönenberg (1954), who examined the cerebrospinal fluid in purulent meningitis, proved the existence of a series of amino acids which are not normally present, and in addition an increase in the concentration of amino acids normally there. In cases of serous meningitis no increase in the amino acids was observed. The conditions for the amino acids thus seem to be very similar to the conditions for uric acid.

SUMMARY

The ratio between the concentration of uric acid in the cerebrospinal fluid and in the plasma is normally about 10 per cent. In purulent meningitis and in tuberculous meningitis this ratio is significantly increased (maximally up to 70—80 per cent). In non-tuberculous serous meningitis there is either no increase at all in the ratio, or only a slight one. The increase of the uric acid seems to vary at a level more or less parallel to the increase in protein content of the cerebrospinal fluid, and it would appear that there is a connection between the increase of the uric acid ratio and the reduction of the glucose concentration in the cerebrospinal fluid.

The uric ratio seems to be a relevant expression of meningeal permeability, and the determination of the uric acid ratio may possibly be of diagnostic value in differentiating between benign serous meningitis and tuberculous meningitis. It is, furthermore, capable of showing in what manner the meningeal permeability changes during the treatment of tuberculous meningitis.

Non-infectious neurological diseases do not ordinarily effect a change in the uric acid ratio.

Acknowledgement.

Miss E. Nødskov is warmly thanked for assisting with the performance of many of the uric acid analyses.

References:

Bene, E. & G. D. Kersley: J. Clin. Path. 1951, *4:* 366.
Berliner, R. W., H. G. Hilton, T. F. Yü & T. J. Kennedy: J. Clin. Invest. 1950, *29:* 396.
Kinsman, J. M. & C. A. d'Alonzo: New Engl. J. Med. 1946, *234:* 459.
Lassen, H. C. A.: Nord. Med. 1942, *16:* 2863.
Lassen, H. C. A. & K. A. Jensen: U.f.L. 1948, *110:* 1069.
Lous, P.: To be published.
Merritt, H. H. & F. Freemont-Smith: The cerebrospinal
Prætorius, E.: Urikase-studier. Copenhagen 1949.
fluid. Saunders. 1938.
Prætorius, E. & H. Poulsen: Scand. J. Clin. & Lab. Invest. 1953, *5:* 273.
Roelsen, E. & M. H. Simesen: Nord. Med. 1942, *13:* 87.
Schönenberg, H.: Ztschr. Kinderheilk. 1954—55, *75:* 301.

CORRELATION BETWEEN HUMAN FOETAL GROWTH AND WATER AND PROTEIN CONTENT OF MATERNAL TISSUES AND BODY FLUIDS

INVESTIGATION OF SIXTY-SIX PREGNANT WOMEN AND THEIR FOETUSES

By P. PAABY

In the following article an account is given of a calculation of the relation between foetal age and foetal length and weight, in 61 human foetuses. A relationship is also demonstrated between the size of the foetus on the one hand and the water and protein content in certain of the tissues and body fluids of the mother on the other hand.

The mothers were hospitalized for therapeutic abortion, and the foetuses were all removed by minor caesarean section, whereby it was possible to obtain for investigation fresh and undamaged foetuses. The indications for the surgical intervention were in most cases psychiatric, and in none of the cases were there grounds for supposing that the reason for the termination of pregnancy had had any significance for the foetal development.

The investigation comprised 66 foetuses. Five foetuses were rejected from the original material because they were abnormal or diseased. Thus, in three cases foetus mortuus was found, in one case the foetus was an anencephalic monster, and in one case the foetus was icteric and oedematous due to the Rhesus phenomenon. The remaining material thus constituted 61 foetuses (see Tabel material thus constituted 61 foetuses (see Table

The age of the foetuses is expressed in days, having been calculated on the basis of the information supplied by the mothers from the first day of the last normal menstruation to the day of operation. All foetuses were measured from vertex to heel in the extended position. The majority of the foetuses were also weighed. Measuring and weighing took place immediately after the removal of the foetus from the uterus.

From the analysis of the regression between the foetal length L in cm and the foetal age A in days, the following expression for the dependence between L and A was calculated: $L = 0.3\ A - 15.4$, valid for approx. $150 > A >$ approx. 70. Fig. 1 shows the repression line, *i. e.*, the length curve. It is fully realized that the "true" length curve in

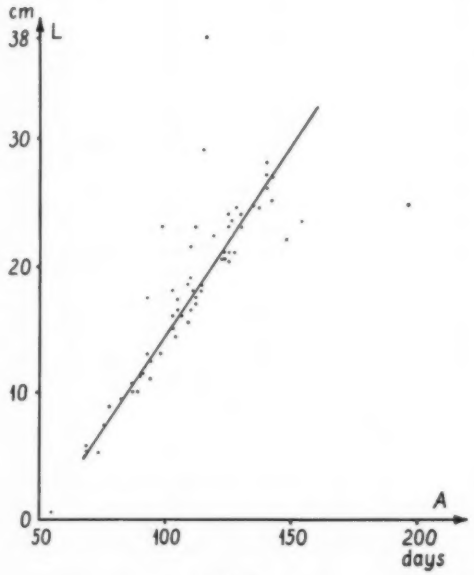

Fig. 1.

Analysis of the regression between foetal length L in cm and age A in days, resulting in the expression: L = 0.3 A — 15.4. Abscissa: A. Ordinate: L. In the regression analysis the cases of extreme deviation in length are omitted for statistical reasons, as it is impossible to be sure of the exact age in these cases. (However, it is considered that the placing of these cases respectively above and below the regression line can be established. See text.)

the age range in question is quite possibly non-linear, but the present material does not justify the setting-up of a more complicated expression for the relationship between L and A.

Forty-six foetuses were weighed exactly. The dependence between foetal weight and age is non-linear, but can in fact be described by two straight lines with an intersection around 100 days. The analysis of the regression between foetal weight in g W and age in days A results in the expression: $W = 1{,}575\ A - 108$, valid for approx. 70 to 100 days, and $W = 6{,}586\ (A\text{-}100) + 46$, valid from 100 to approx. 150 days. See Fig. 2.

The dispersion around the regression lines in Figs. 1 and 2 can be due to: a) uncertainty in the mother's statement as to the length of the menostasia. It would be more satisfactory to know the time of ovulation, copulation or conception. (Mall 1918, Streeter 1921, Grosser 1932). This was unobtainable.

From the Central Laboratory, Aalborg Municipal Hospital. Chief: *H. O. Bang.*

The statistical work has been carried out in collaboration with Civil Engineer *Ole Nielsen*, Laboratory Director.

The patient material originates from Aalborg County Hospital, Surgical Department, and Aalborg Municipal Hospital, Surgical Department.

The work has been aided by a grant from *King Christian X's Foundation.*

Table 1.

Menostasis in days	Foetal length in cm	Foetal weight in g	Skin		Fascia		Musculature		Whole blood		Hb%	Serum	
			H_2O% w.w.	Prot.% w.w.	H_2O% w.w.	Prot.% w.w.	H_2O% w.w.	Prot.% w.w.	H_2O% w.w	Prot.% w.w.		H_2O% w.w.	Prot.%
55	0.6	0,0256									90		
69	5.5					24.5					85		5.9
69	5.75	5.2	68.0	32.6	71.8	20.9	74.5	19.2	81.66	17.8	80		6.4
74	5.2	3.95	66.3	37.5	75.2	25.0	77.0	20.6			70	92.1	5.5
76	7.6	11.4	69.5	29.1	73.7	24.0	75.7	20.6	79.8	19.5	83		5.4
78	8.8	16.6							78.6	17.7	95		6.1
83	9.5	18.0	61.8	35.0	76.4	23.1	76.9	19.8	82.0	16.9	72		6.5
87	10.0	37.0				18.7					90		5.8
87	10.75	27.8	69.3	31.2	79.0	19.65	76.2	20.0	81.4	18.0	68		6.7
89	10.0					21.3					80		5.6
90	11.25	30.0				22.0					94		5.9
91	11.5	32.0	68.7	32.5	71.0	25.3	73.1	19.0	81.5	16.9	83		6.2
93	13.0	46.3			75.5	23.0	76.8	20.0			80	92.2	5.5
93	17.5	106.0	71.4	26.5	77.2	22.2	72.6	18.1	82.2	15.6	83		
94	11.0	31.5									83		
94	12.5	41.0	73.0	25.0	74.4	23.0	74.6	23.0	81.3	17.1	82		6.2
98	13.0	50.0				20.2					79		5.5
99	23.0					22.1					79		5.1
103	15.0					21.0					98		5.1
103	16.0	64.8	71.8	26.3	78.9	19.4	77.6	18.8			73	92.1	5.3
103	18.0	104.0	70.0	27.0	79.0	21.5	78.0	19.1	83.0	16.2	77		5.8
104	16.5	83.0			74.8	24.4	76.9	19.4			54	92.7	5.6
104	14.3	60.0	69.27	28.7	72.85	22.8	77.8	20.0	82.07	17.95	77	92.04	5.8
105	17.25	95.0	70.2	28.9	75.7	22.4	75.4	19.5	81.6	17.45	70		6.4
106	16.0					21.3					78		5.7
109	15.5					20.2					92		5.1
109	18.5	125.0	66.8	31.3	76.8	22.5	74.5	20.6	81.9	18.1	78		6.4
110	19.0					23.6					58		5.8
110	21.5	195.0			77.5	23.1	76.2	17.5			60	91.9	5.9
110	16.5	91.0			76.2	22.5	74.0	20.0			70	92.3	5.2
111	18.0					19.8					76		5.7
112	23.0	230.0	68.2	31.6	75.9	22.8					68	92.5	5.6
112	17.5	115.0	69.3	30.3	70.5	20.2	72.0	22.5	80.6	17.7	91		6.0
112	17.0	95.0	73.9	25.6	75.3	18.8	74.7	18.3	81.4	16.5	76		6.5
114	18.5	125.0	71.5	29.4	77.0	23.1	68.5	17.5	82.9	18.8	82		5.5
114	18.0	115.0	71.1	30.4	75.3	23.7	77.7	20.2	81.0	18.55	83		7.1
115	29.0	435.0	78.0	22.0	79.3	20.6	71.5	20.0	82.3	16.3	80		6.0
116	38.0					20.0					78		5.6
119	22.3	225.0	68.45	27.0	77.2	22.5	78.3	19.0	82.55	15.9	77		6.0
123	20.5	162.0	64.2	36.6	74.5	22.4	76.2	19.5	81.5	17.05	80		6.1
123	21.5	190.0	74.61	26.7	75.88	22.85	76.65	19.7	81.38	18.2	80	91.5	6.5
123	20.5	170.0	68.63	31.2	75.6	23.4	75.34	20.3	82.04	17.16	79	91.93	6.4
125	24.0					20.6					80		5.2
125	23.0	175.0				15.6					86		5.1
125	21.0	75.0			65.0	32.5	77.0	15.6			70	91.2	5.6
125	20.3	183.0	69.44	28.9	76.65	21.38	75.77	20.36	81.26	18.5	83	91.2	6.5
126	23.5	250.0									84		5.5
127	21.0					19.5					74		6.2
128	24.5	290.0				15.1					70		5.7
130	23.0	220.0				22.5					82		5.0
133	24.0	290.0				21.0					87		5.6
135	24.75	298.0	67.6	32.2	75.18	22.1	77.5	19.9	81.08	18.2	82	91.36	6.2
137	24.5	285.0				20.5					78		6.0
140	26.0					18.2					97		5.7
140	27.0	320.0				23.5					88		5.8
140	28.0	405.0				15.2					75		5.4
142	25.0	335.0				21.4					82		4.8
142	27.0	295.0				21.0					85		5.8
148	22.0					19.5					53		5.5
154	23.5	293.0	70.05	29.3	75.1	20.7	76.65	18.7	80.36	20.5	87	91.33	6.0
196	24.5					19.0					79		5.1

The table gives the size and weight of 61 foetuses and the results of the analyses carried out on the tissues and body fluids of the mothers. H_2O % w.w. signifies the water content in percentage of wet weight. (The protein content in percentage of dry weight, estimated by direct analysis, is not included in the table for considerations of space, but can easily be calculated by means of the formula:

% w.w. = % d.w. $(1 - \frac{H_2O\%}{100}) . \frac{\text{Protein}}{H_2O}$%, which is referred to in the text, can also be calculated on the basis of the figures in the table.

b) Uncertainty in the length measurement. The foetuses were measured in the outstretched position with a rigid measuring scale, but even in fresh foetuses in which the tone was retained, the tendency to yield on the part of the extremities and cranium can give a certain measuring uncertainty.

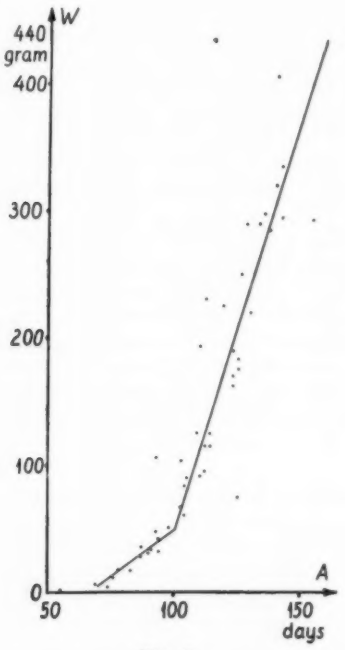

Fig. 2.

Analysis of the regression between foetal weight W in gm and age A in days, resulting in the expressions W W = 1,575 A — 108 for 100 ≧ A approx. 70 and = 6,586 (A-100) + 46 for approx. 150 > A ≧ 100. In the regression analysis itself the cases of extreme deviation in weight are omitted, as it is impossible to be sure of the age stated in such cases. (On the other hand, it is considered that the placing of these cases respectively above and below the regression line is certain enough. See text.)

c) Uncertainty in weighing, which for example can be due to loss of blood from the foetus in those cases where the umbilical cord was torn during operation, or due to interchange of blood in uncertain amounts between the foetal circulation and the placental circulation before the umbilical cord was tied.

d) The varying magnitude of diverse known and unknown factors affecting the growth of the foetus, *e. g.*, genetic constitution, sex and conditions of growth.

Those points which deviate most as is mentioned in the text to Figs. 1 and 2, are omitted for statistical reasons in the calculation of the regression coefficient. Later in the text an account is given as to how, by means of the regression line, the foetuses are grouped into those cases which lie above and below "mean" size. If, for example, one considers the point corresponding to 115 days and 38 cm in Fig. 1 as representing a foetus whose age has presumably been given incorrectly, the probability that this foetus is larger than the "mean", and should therefore be placed above the regression line, seems nevertheless great enough to include it in the distribution of the material by means of the regression lines, as indicated later. Therefore, so as not reduce the material unnecessarily by rejecting otherwise normal foetuses, the cases deviating most above and below the regression lines are also included in this distribution.

The expressions calculated here for the growth of the foetus can be compared with those given by A r e y in 1946. The foetuses in the author's material are somewhat longer than those quoted by A r e y. Measured by age, the difference amounts to fully one week. Also as far as the weight is concerned the foetuses in the author's material are a little heavier than A r e y's. The difference is perhaps due to the fact that the foetuses in the author's material originate exclusively from normal pregnancies, and were all fresh.

On the basis of an earlier work (P a a b y 1955), it was conjectured that possibly a relationship between the protein content in the mother's tissue and the growth of the foetus existed. The protein and water content in the skin, fascia, musculature, whole blood and serum of as many mothers as possible was therefore investigated. The haemoglobin percentage of the mothers was also investigated. In a number of cases the serum protein was investigated by means of fractionating with paper-electrophoresis.

All blood tests were taken on the day of operation — 12 to 18 hrs. after the arrival of the patient in hospital — during the morning, while the patient was fasting and in bed (L a n g e 1946). Tissue samples were taken from the operation wound in the abdominal wall at the commencement of the operation, and sent immediately to the laboratory in small close-fitting jars. Here they were cleansed and weighed. The samples taken were as a rule around ¼ cm^2 with a weight of up to a couple of hundred mg. The samples were divided into several pieces, and estimations of both the water content with a subsequent nitrogen estimation of the dried sample, and a direct nitrogen estimation on an undried "wet" sample, were carried out. The results of the two nitrogen estimations were compared. The drying was carried out in a vacuum drying oven for 16 hrs. at 70°C and 23 mm Hg. An analytical balance of type Mettler with an accuracy of 0.1 mg was used for the weighing. Special small weighing jars with close-fitting lids were used for holding the samples during the weighing and drying. The nitrogen estimations were carried out by means of the Kjeldahl method (K j e l d a h l 1888), modified as a micromethod (N i e d e r l & N i e d e r l 1942, H a m m a r s t e n 1947). In a few cases the nitrogen estimation was carried out as a micro-Kjeldahl modified according to C o n w a y (Conway 1950). The protein content was estimated as nitrogen content multiplied by 6.25. The serum protein was estimated by means of the copper sulphate method (P h i l i p s, V a n S l y k e et al., 1950). An account is given in an

Table 2.

Distribution according to foetal weight.

	H_2O % w. w.	Protein % w. w.	$\frac{\text{Protein}}{H_2O}$ %	Protein % d. w.
Mother's skin	$\bar{x}_o > \bar{x}_u$ 70.32 > 69.17 P = 0.15	$\bar{x}_o < \bar{x}_u$ 28.22 < 30.83 P = 0.035	$\bar{x}_o < \bar{x}_u$ 40.36 < 44.80 P = 0.05	$\bar{x}_o < \bar{x}_u$
Mothers's fascia	$\bar{x}_o > \bar{x}_u$ 76.37 > 74.43 P = 0.025	$\bar{x}_o < \bar{x}_u$ 21.21 < 22.41 P = 0.09	$\bar{x}_o < \bar{x}_u$ 29.09 < 31.15 P = 0.08	$\bar{x}_o > \bar{x}_u$
Mother's musculature	$\bar{x}_o > \bar{x}_u$ 75.72 > 75.35 P = 0.3	$\bar{x}_o < \bar{x}_u$ 19.5 < 19.6 P = 0.3	$\bar{x}_o < \bar{x}_u$ 25.78 < 26.01 P = 0.4	$\bar{x}_o > \bar{x}_n$
Mother's blood	$\bar{x}_o > \bar{x}_u$ 81.63 > 81.37 P = 0.25	$\bar{x}_o < \bar{x}_u$ 17.04 < 18.04 P = 0.01	$\bar{x}_o < \bar{x}_u$ 20.89 < 22.18 P = 0.02	$\bar{x}_o < \bar{x}_u$
Mother's hb. %		$\bar{x}_o < \bar{x}_u$ 78.0 < 80.5 P = 0.15		
Mother's serum	$\bar{x}_o > \bar{x}_u$ 92.13 > 91.68 P = 0.04	$\bar{x}_o < \bar{x}_u$ 5.79 < 5.97 P = 0.09	$\bar{x}_o < \bar{x}_u$ 6.15 < 6.5 P = 0.08	

Table 2

The table shows the result of the analyses of tissue and body fluids of mothers of the weight-determined foetuses.

$\bar{x}_o$ = *mean value of the analyses of tissues from mothers of foetuses over mean weight.*

$\bar{x}_u$ = *mean value of the analyses of tissues from mothers of foetuses under mean weight.*

P *gives the significance of* ($\bar{x}_o - \bar{x}_u$) *estimated by the t-test.*

earlier work of the electrophoresis technique used (Bang & Paaby 1955). The haemoglobin estimations were carried out by photometric reading in a Haemotest, after diluting the blood with ammonia water. All analyses, weighings, etc. were double estimations and in many cases triple estimations. The results shown in Table 1 are always mean values of at least 2 analyses.

As mentioned, one of the purposes of the work was to investigate whether a relationship existed between the foetal growth and the protein- and water-content in the tissues and body fluids of the mother. The foetuses were therefore divided into two groups, one group comprising foetuses which had greater length and weight than those values calculated for each age in question according to the equations set up for the relationships between L, V and A, and one group containing smaller foetuses. It was therefore only necessary to divide the material by means of the regression lines into those cases lying above and those cases lying below the regression lines. See Figs. 1 and 2. As expected, it turned out that some of the cases which lay above the regression line as far as weight was concerned lay below the regression line as far as length was concerned, and vice versa. It was therefore decided to investigate the length-determined and weight-determined foetuses separately.

The investigation, accordingly, concerns the result of the analyses carried out on skin, fascia, musculature, whole blood and serum from mothers of those foetuses which "lie" above the regression line, and which are referred to in what follows by the symbol "*o*" and from mothers of those foetuses which as far as length and weight are concerned "lie" under the regression line. These are referred to in what follows by the symbol "*u*". In Tables 2 and 3 a survey is given of the results of the analyses of the haemoglobin percentage as well as of the content of water and protein in the tissue, blood and serum of the mothers, the mothers being grouped in accordance with both the weight-determination and the length-determination of their foetuses. In the tables, $\bar{x}_o$ signifies in each case the mean value found in the analyses for those mothers whose foetuses were over the mean with respect to

Table 3.

Distribution according to foetal length.

	H_2O % w. w.	Protein % w. w.	$\frac{\text{Protein}}{H_2O}$ %	Protein % d. w.	$\frac{\text{Protein}}{H_2O}$ % after parallel-displacement of the regression line. See text.
Mother's skin	$\bar{\times}_o > \bar{\times}_u$ $70.5 > 68.9$ $P = 0.1$	$\bar{\times}_o < \bar{\times}_u$ $28.35 < 30.9$ $P = 0.03$	$\bar{\times}_o < \bar{\times}_u$ $40.39 < 45.09$ $P = 0.05$	$\bar{\times}_o < \bar{\times}_u$	$\bar{\times}_o < \bar{\times}_u$ $40.2 < 44.3$ $P = 0.07$
Mother's fascia	$\bar{\times}_o > \bar{\times}_u$ $76.54 > 74.13$ $P = 0.01$	$\bar{\times}_o < \bar{\times}_u$ $21.2 < 21.8$ $P = 0.18$	$\bar{\times}_o < \bar{\times}_u$ $28.96 < 31.38$ $P = 0.06$	$\bar{\times}_o > \bar{\times}_u$	$\bar{\times}_o < \bar{\times}_u$ $28.9 < 31.04$ $P = 0.07$
Mother's musculature	$\bar{\times}_o > \bar{\times}_u$ $75.7 > 75.29$ $P = 0.3$	$\bar{\times}_o < \bar{\times}_u$ $19.39 < 19.7$ $P = 0.25$	$\bar{\times}_o < \bar{\times}_u$ $25.6 < 26.2$ $P = 0.3$	$\bar{\times}_o < \bar{\times}_u$	$\bar{\times}_o < \bar{\times}_u$ $25.38 < 26.24$ $P = 0.12$
Mother's blood	$\bar{\times}_o > \bar{\times}_u$ $81.5 > 81.46$ $P > 0.5$	$\bar{\times}_o < \bar{\times}_u$ $17.3 < 17.9$ $P = 0.1$	$\bar{\times}_o < \bar{\times}_u$ $21.8 < 21.9$ $P > 0.5$	$\bar{\times}_o < \bar{\times}_u$	$\bar{\times}_o < \bar{\times}_u$ $20.66 < 22.11$ $P = 0.01$
Mother's hb. %		$\bar{\times}_o < \bar{\times}_u$ $76.4 < 81.4$ $P = 0.015$			$\bar{\times}_o < \bar{\times}_u$ $76.0 < 81.2$ $P = 0.03$
Mother's serum	$\bar{\times}_o > \bar{\times}_u$ $92.15 > 91.68$ $P = 0.04$	$\bar{\times}_o < \bar{\times}_u$ $5.7 < 5.8$ $P = 0.2$	$\bar{\times}_o < \bar{\times}_u$ $6.15 < 6\,5$ $P = 0.08$		$\bar{\times}_o < \bar{\times}_u$ $6.15 < 6.50$ $P = 0.08$

Table 3.

The table shows the result of the analyses of tissue and body fluids of mothers of length-determined foetuses.

$\bar{\times}_o$ = *mean value of analyses of tissues from mothers of foetuses over mean length.*

$\bar{\times}_u$ = *mean value of analyses of tissues from mothers of foetuses under mean length.*

P *gives the significance of* ($\bar{\times}_o - \bar{\times}_u$) *estimated by the t-test.*

lenght and weight (the points above the regression line in Figs. 1 and 2). Correspondingly, $\bar{\times}_u$ signifies the mean value for analyses on those mothers whose foetuses were under the mean length and mean weight.

As appears from Table 1, the number of length-determined and weight-determined foetuses was not the same. In addition, it is seen that a number of the cases which were over the mean as far as with both the weight-determination and the the weight was concerned were under the mean in respect to length. Furthermore, not quite the same analyses were carried out on the same mothers in all cases. In view of these circumstances, one can say with some justification that from a larger total "statistical population" a number of different "materials" has been arbitrarily selected for investigation. Should the results of such a series of investigations be in agreement throughout, therefore, this in itself would speak for the validity of the results.

Tables 2 and 3 show that as far as water-content in percentage of wet weight is concerned, $\bar{\times}_o$ in all cases lies over $\bar{\times}_u$, *i. e.,* those mothers who had had the largest foetuses had the most water in their tissues and body fluids.

As far as protein content as a percentage of wet weight is concerned, $\bar{\times}_o$ in all cases lies under $\bar{\times}_u$, *i. e.,* those mothers who had had the largest foetuses had the lowest protein content in their tissues and body fluids. High water content is thus always accompanied by low protein content.

The ratio between protein and water expressed as a percentage gives a picture of the ratio between these two constituents which is independent of variations in the content of fat, carbohydrate and minerals in the tissues. Here also $\bar{\times}_o$ is in all cases less than $\bar{\times}_u$.

As haemoglobin is a protein, the haemoglobin percentage as was to be expected follows that of the protein, and here also in all cases $\bar{\times}_o$ is found to be less than $\bar{\times}_u$.

The values of "P" shown in Tables 2 and 3 indicate the significance level, as determined by the t-test (Bernstein & Weatherall 1952). In the case of the musculature, "significance" can nowhere be established. In the majority of the other cases the significance level must be con-

Table 4.

Distribution according to foetal weight.

Absolute % of:	Albumin	α_1 -globulin	α_2 -globulin	β -globulin	γ -globulin
Electrophoresis of mother's serum	$\bar{x}_o < \bar{x}_u$ 2.88 < 2.98 P = 0.12	$\bar{x}_o < \bar{x}_u$ 0.419 < 0.456 P = 0.09	$\bar{x}_o > \bar{x}_u$ 0.737 > 0.735 P > 0.3	$\bar{x}_o < \bar{x}_u$ 0.917 < 0.937 P > 0.3	$\bar{x}_o < \bar{x}_u$ 0.97 < 1.05 P = 0.15
Relative % of:	**Albumin**	**α_1 -globulin**	**α_2 -globulin**	**β -globulin**	**γ -globulin**
Electrophoresis of mother's serum	$\bar{x}_o > \bar{x}_u$ 48.5 > 48.14	$\bar{x}_o > \bar{x}_u$ 7.39 > 7.07 P = 0.18	$\bar{x}_o > \bar{x}_u$ 12.38 > 12.11	$\bar{x}_o > \bar{x}_u$ 15.43 > 15.29	$\bar{x}_o < \bar{x}_u$ 16.31 < 17.51 P = 0.15

Table 4.

The table shows the results of the electrophoresis of serum from mothers of the 30 weight-determined foetuses. The meaning of $\bar{x}_o$, $\bar{x}_u$ and P is the same as in Tables 2 and 3.

sidered as satisfactory, not least in the consideration of the fact that biological material is involved, where so many unknown factors can give rise to variations.

Still another statistical evaluation may be advanced: as far as the skin, fascia, musculature, blood and serum are concerned, *i. e.*, 5 different "tissues", ($\bar{x}_o - \bar{x}_u$) has the same sign, namely + ve with respect to the water and —ve with respect to the protein. The probability of this arising by chance is $(\frac{1}{2})^5$, *i. e.*, negligible. This shows that the variation in the content of water and protein is parallel in the skin, fascia, musculature, blood and serum, and signifies furthermore that even though the P-value in the case of muscle, for example, is not significant, weight should be laid nevertheless on the difference found between $\bar{x}_o$ and $\bar{x}_u$ even in this case.

When considering Fig. 1, it will be observed that a number of the points lying above the regression line lie for all practical purposes on the line. If one now displaces the regression line parallel to itself very slightly upwards, so that the points mentioned come to lie under the line, one obtains an arbitrary division of the material into a lesser group of the very largest foetuses and a greater but more uniform group of average sized and smaller foetuses. To avoid too many calculations, it has been considered sufficient in this case to calculate $\bar{x}_o$ and $\bar{x}_u$ for the haemoglobin percentage and protein/H_2O percentage, which latter on the other hand gives an expression for the variations between two of the tissue components investigated. The result is shown in the column on the extreme right of Table 3. It will be seen that the significance level for skin, fascia, haemoglobin percentage and serum remains at an unchanged high level, while the significance level for musculature and blood is raised.

Finally, Tables 2 and 3 show the results of the investigations of the protein content of the various tissues in percentage of dry weight*). It will be noted that there is no agreement between the various tissues investigated. This can either be due to the fact that on the basis of the division of the material as here carried out no certain difference between $\bar{x}_o$ and $\bar{x}_u$ is to be found, as far as concerns the protein content in percentage of dry weight**), or it can be due to differences arising during the cleansing of the tissue samples of fat. Blood, for example, cannot be dissected, skin is easy to dissect free of fat, while fascia and musculature are difficult to cleanse from that fat which lies between the individual fibres in the tissue.

Serum protein from 30 of the mothers was fractionated by means of paper-electrophoresis. The relative distribution of the different protein fractions is shown in Table 4, as well as their absolute amounts. The 30 mothers were distributed according to the weight of the foetuses, with 14 in group "o" and 16 in group "u". The absolute amounts of serum protein fractions are distributed, as was expected, in essentially the same way as the total amount of serum protein, *i. e.*, $\bar{x}_o < \bar{x}_u$ As far as the relative distribution of the serum-protein fractions is concerned, it is seen that in the case of gamma-globulin $\bar{x}_o < \bar{x}_u$, while in the case of the other fractions $\bar{x}_o > \bar{x}_u$. The significance level in this case, however, is not convincing.

DISCUSSION

The evaluation of the results of the investigations remains speculative. Those factors which

*) During the drying, the largest component of the tissue is removed, that is, the water. The protein content as a percentage of the dried weight is therefore dependent on the ratio between the protein and the amount of minerals, carbohydrate and in particular fat in the dried sample.

**) There are no grounds to expect that the ratio between protein and fat should be the same as the ratio between protein and water.

can change the relationship between protein and water in the organism are, among other things, partly nutritional, partly hormonal. Inadequate protein nutrition can produce a tendency to oedema (K e y s et al., 1950. Ecology of Health 1949), and hereby increase the water content of the mother's tissues, but it is difficult to see how this can be linked up with great foetal growth. On the contrary, there appear to be standpoints for assuming that adequate protein nourishment is of significance for great foetal growth (E b b s et al., 1941. B u r k e et al., 1943. M c C a n c e et al., 1951).

The water content of the organism in pregnancy rises at the commencement of pregnancy, which is possibly an effect of the placental hormone production (M a c k 1955), but can also be considered as being an effect, for example, of the hormone production of the hypophysis (ACTH). Finally, an interaction can be imagined between the hormone-producing tissue of the mother and ovum. If the same hormone or hormone complex which influences the retention of water is also conceived as directing the growth of the fetus, the interplay between great fetal growth and high water percentage in the mother's tissue becomes understandable. The lower protein content as percent of wet weight and the lower haemoglobin percentage might be considered mainly as a consequence of the increased water content.

An exhaustive explanation on the basis of the present investigations cannot be given.

SUMMARY

An account is given of an investigation of the size and weight of 61 fresh undamaged and normal human foetuses. Expressions are calculated for the change in length and weight of the foetuses with the increasing age of the foetus.

It is shown that in the skin, fascia, musculature, whole blood and serum of the mothers of the longest and heaviest foetuses there is more water and less protein — as well as lower haemoglobin percent — than in the same tissues and body fluids from mothers to the shortest and lightest foetuses. A statistical analysis gives the significance level. The differences found must be considered as real.

An account of the method of analysis is given and the results found are discussed. In a subsequent article an account will be given of a series of analyses of water and protein in the tissues and various organs of the foetuses.

References:

Arey 1946, quoted in: Sunderman, F. W. and F. Boerner: Normal Values in Clinical Medicine. W. B. Saunders Company, Philadelphia 1950, p. 422.

Association of Official Agricultural Chemists: Official and Tentative Methods of Analysis 1945, 6. ed., p. 238.

Bang, H. O. and *P. Paaby:* Nord. Med. 1955, *54:* 1693.

Bernstein, L. and *M. Weatherall.* Statistics for Medical and Other Biological Students. E. & S. Livingstone Ltd., Edinburgh 1952.

Burke et al.: J. Pediatrics 1943, *23:* 506.

Conway, E. J.: "Microdiffusion Analysis and Volumetric Error", Crosby, Lockwood and Son, London 1950.

Ebbs et al.: J. Nutr. 1941, *22:* 515.

"Ecology of Health", The Commonwealth Fund, New York 1949, p. 53.

Grosser, O.: Anat. Anzeiger 1932, *20:* 479.

Hammarsten, G.: "Kliniska Laborationsmetoder", Astra, Södertälje, 1947, p. 317.

Kjeldahl, J.: "En ny metode til kvælstofbestemmelse i organiske stoffer". Medd. fra Carlsberglaboratoriet II, København 1888.

Keys et al.: Human Starvation II. Minnesota Press 1950, *II:* 420.

Lange, H. F.: Acta Med. Scand. 1946, *125:* suppl. CLXXVI.

Mall, F. P.: Am. Journ. Anat. 1918, *23:* 397.

Mack, H. C.: The Plasma Proteins in Pregnancy. Charl. Thomas, Springfield, Illinois, 1955, p. 30.

McCance et al.: Medical Research Council. Spec. Rep. Series 1951, *275:* 404.

Niederl, J. B. and *V. Niederl:* Organic Quantitative Microanalysis. John Wiley and Son, New York, 1942, 2. ed., p. 68.

Paaby, P.: Dan. Med. Bull. 1955, *2:* 143.

Philips, Van Slyke et al.: J. Biol. Chem. 1950, *183:* 305.

Streeter, F. L.: Contributions to Embryology, 1921, *47:* 145.